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SERUM CALCIUM AND INORGANIC PHOSPHATE IN THE NEWBORN INFANT, AND THEIR RELATION TO DIFFERENT FEEDINGS

GEORGE G. GRAHAM, M.D., LEWIS A. BARNESS, M.D., AND PAUL GYÖRGY, M.D.
PHILADELPHIA, PA.

INTEREST in the calcium-phosphorus ratio has been renewed by studies of the etiology of "newborn" tetany, and by the recently renewed suggestion that the high phosphate intake of artificial feeding is one of the contributory causes of tetany.[1, 2] The present work was undertaken to study the response of serum calcium and inorganic phosphate to the types of milk given the newborn infant.

METHOD

The subjects of this study were all full-term, apparently healthy, infants, taken at random from the same nursery. Those that were breast-fed were in no way different from those artificially fed. Those receiving breast milk plus a supplement were usually smaller full-term infants whose mothers' breast milk supply was not adequate.

Blood samples were taken at different times during the day, nearly always midway between two feedings. Two hundred forty blood samples were taken by heel puncture from seventy-nine infants at repeated intervals in the first five days of life and thereafter. Serum inorganic phosphate determinations were done on all of these, and serum calcium was also determined in 156 of the samples. For the phosphate determination the method of Fiske and Subbarow,[3] adapted to 0.1 ml. of serum, was used; for calcium, the method of Sendroy[4] was used for which also 0.1 ml. of serum is sufficient.

Five different feeding schedules were used:

1. Breast milk alone.
2. The standard modification of cow's milk, prepared with evaporated milk and sugar, and hereafter referred to as evaporated milk.*
3. An artificial preparation which duplicates the chemical composition of human colostrum, and hereafter referred to as artificial colostrum.†
4. Breast milk supplemented with the evaporated milk formula.
5. Breast milk supplemented with the artificial colostrum preparation.

None of the infants received any vitamin supplement. The evaporated milk used contains 400 U. vitamin D per one quart of formula.

From the Department of Pediatrics, School of Medicine, University of Pennsylvania.

*Reconstituted evaporated milk contained, per 100 ml., protein 2.8 Gm., carbohydrate 7.0 Gm., fat 5.6 Gm., calories 68.

†See footnote, page 402.

RESULTS

In Table I are listed the inorganic phosphate values as milligrams of phosphorus per 100 ml. of serum. They have been tabulated according to the feeding and the age of the infant in days, and the totals are those for each feeding schedule. In each category are listed the number of observations, their range, their mean value, and when there were enough observations, the standard deviation from the mean.

The values listed as "fasting" were usually obtained from infants who had received glucose in water. An attempt was made to determine if these glucose feedings, or strict fasting, altered the serum phosphate. The differences, if any, were well within the possible error of the method.

The range of values for breast-fed infants (3.9 to 7.8 mg. P) as well as for those fed artificial colostrum (4.0 to 7.8) and breast plus artificial colostrum (4.8 to 6.9) is a fairly narrow one, particularly when any one infant was followed; for evaporated milk, however, it is much wider (6.0 to 12.8), and very often individual infants showed marked day-to-day variations. In this last group there was a marked tendency for the serum phosphate to rise rapidly from the fasting level to high values in the third, fourth, and fifth days of life, and then gradually decrease. In a number of infants fed evaporated milk who were followed for ten days and over, serum phosphate levels were seen to approximate the values for breast-fed infants during the second week of life. In a few infants who were on breast milk or artificial colostrum, and were changed to evaporated milk in the second or third week, the serum phosphate, which was originally in the normal range,

†This preparation was furnished by Wyeth Incorporated. It had the following composition, giving also the comparative data for human colostrum (one to five days) and human transitional milk (five to ten days):

	EXPERIMENTAL FORMULA	HUMAN COLOSTRUM (1 – 5 DAYS)	HUMAN TRANSITIONAL MILK (5 – 10 DAYS)
Total solids	13.01 Gm.[3]	12.8 Gm.	13.6 Gm.
Calories	71.7	58	74
Lactose	6.38 Gm.[3]	5.3 Gm.	6.6 Gm.
Fat	3.50 Gm.[3]	2.9 Gm.	3.6 Gm.
Protein	2.50 Gm.[3]	2.7 Gm.	1.6 Gm.
Ash	330.0 mg.[3]	330.0 mg.	240.0 mg.
Calcium	43.0 mg.[3]	31.0 mg.	34.0 mg.
Sodium	30.0 mg.[3]	48.0 mg.	29.0 mg.
Magnesium	4.6 mg.[3]	4.0 mg.	4.0 mg.
Potassium	88 mg.[3]	74.0 mg.	64.0 mg.
Phosphorus	26.0 mg.[3]	14.0 mg.	17.0 mg.
Copper	0.05 mg.[3]	0.06 mg.	–
Iron	0.1 mg.[3]	0.12 mg.	–
Citric acid	55 mg.	–	–
Ascorbic acid	5 mg.[3]	4.4 mg.	5.4 mg.
Riboflavin	0.034 mg.[3]	0.031 mg.	0.037 mg.
Thiamine hydrochloride	0.025 mg.[3]	0.019 mg.	0.006 mg.
Niacinamide	0.17 mg.[3]	0.075 mg.	0.175 mg.
Calcium Pantothenate	0.3 mg.[3]	0.183 mg.	0.288 mg.
Choline hydrochloride	9.0 mg.[3, 4]	–	–
Folic acid	0.0003 mg.[3, 4]	–	–
Pyridoxine hydrochloride	0.02 mg.[3]	–	–
Inositol	40.0 mg.[3, 4]	–	–
Carotene	0.066 mg.[3, 4]	0.112 mg.	0.038 mg.
Vitamin A	362 USP units[3]	207 USP units	204 USP units
Vitamin D	39.6 USP units[3]	–	–
Vitamin E	1.3 mg.[3]	1.28 mg.	1.32 mg.

[1]Bulletin of the National Research Council, No. 119.
[2]Values determined by analysis.
[3]Values calculated from master formula.
[4]Bulletin of the National Research Council, No. 119, value for mature human milk.

TABLE I. INORGANIC SERUM PHOSPHATE (AS MG. OF P/100 ML. OF SERUM), ACCORDING TO THE TYPE OF MILK GIVEN NEWBORN INFANTS

FEEDING	AGE IN DAYS							
	0	1	2	3	4	5	6-21	TOTAL
Fasting	(11)*	(12)						(23)
Range	4.7 – 6.2	4.4 – 6.8						4.4 – 6.8
Mean	5.7 ± 0.52†	5.7 – 0.67						5.7 ± 0.59
Breast (B)		(11)	(12)	(10)	(9)	(14)	(5)	(61)
Range		5.5 – 6.7	5.7 – 7.8	4.8 – 6.6	5.0 – 7.5	3.9 – 6.6	5.4 – 7.4	3.9 – 7.8
Mean		6.2 ± 0.55	6.3 ± 0.59	6.1 ± 0.58	6.0 ± 0.54	5.8 ± 0.80	6.5	6.1 ± 0.67
Evaporated (E)		(7)	(13)	(7)	(9)	(8)	(12)	(56)
Range		6.0 – 8.8	6.5 – 9.7	7.0 – 12.0	7.2 – 12.8	7.6 – 10.2	6.9 – 8.8	6.0 – 12.8
Mean		7.2 ± 0.90	8.0 ± 0.92	8.8 ± 1.57	8.8 ± 1.56	8.6 ± 0.73	7.8 ± 0.76	8.2 ± 1.23
Colostrum (C)		(6)	(9)	(13)	(10)	(10)	(5)	(53)
Range		4.0 – 7.1	5.4 – 7.0	4.3 – 7.5	5.7 – 7.3	4.6 – 7.6	6.0 – 7.8	4.0 – 7.8
Mean		5.9 ± 1.04	6.3 ± 0.52	6.4 ± 0.85	6.6 ± 0.57	6.7 ± 0.87	6.78	6.5 ± 0.81
(B) + (E)		(4)	(7)	(6)	(7)	(5)	(4)	(33)
Range		5.8 – 7.7	6.4 – 8.8	5.7 – 7.9	6.1 – 8.6	7.0 – 8.2	6.3 – 8.0	5.7 – 8.8
Mean		6.85	7.4 ± 0.80	6.9 ± 0.79	7.1 ± 0.76	7.50	7.12	7.2 ± 0.79
(B) + (C)		(3)	(2)	(3)	(3)	(3)		(14)
Range		5.4 – 6.5	4.8 – 6.3	5.0 – 6.9	5.7 – 6.6	5.2 – 6.2		4.8 – 6.9
Mean		5.77	5.55	6.00	6.07	5.73		5.8 ± 0.68

*Bracket numbers indicate number of observations.
†Numbers following mean are standard deviations.

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TABLE II. SERUM CALCIUM (IN MG./100 ML. OF SERUM) ACCORDING TO THE TYPE OF MILK GIVEN NEWBORN INFANTS

FEEDING	AGE IN DAYS						
	0-1	2	3	4	5	6-21	TOTAL
Fasting	(10)*						(10)
Range	9.2 – 11.0						9.2 – 11.0
Mean	10.15 ± 0.54 †						10.15 ± 0.54
Breast (B)	(4)	(6)	(4)	(6)	(8)	(5)	(33)
Range	10.0 – 11.6	9.0 – 11.2	10.3 – 11.4	8.9 – 11.3	8.4 – 10.9	9.5 – 11.2	8.4 – 11.6
Mean	10.45	10.30	10.75	10.30	9.95	10.34	10.29 ± 0.74
Evaporated (E)	(3)	(9)	(7)	(7)	(8)	(7)	(41)
Range	9.4 – 9.8	8.5 – 12.6	9.6 – 11.9	8.9 – 10.9	8.1 – 11.5	8.7 – 10.6	8.1 – 12.6
Mean	9.63	10.14	10.67	9.93	9.15	10.00	9.94 ± 1.04
Colostrum (C)	(6)	(8)	(9)	(7)	(7)	(5)	(42)
Range	9.6 – 11.1	9.4 – 10.8	8.9 – 11.5	8.9 – 11.0	8.8 – 11.6	9.5 – 11.5	8.8 – 11.6
Mean	10.32	10.04	10.02	10.07	9.63	10.34	10.05
(B) + (E)	(3)	(4)	(4)	(4)	(4)	(1)	(20)
Range	9.6 – 11.0	8.5 – 10.1	9.0 – 9.6	9.3 – 10.7	9.5 – 10.1	10.6	8.5 – 11.0
Mean	10.40	9.40	9.28	9.83	9.73	10.6	9.74 ± 0.63
(B) + (C)	(3)	(1)	(2)	(2)	(2)		(10)
Range	8.6 – 9.9	9.6	9.4 – 9.6	9.8 – 11.0	9.9 – 10.3		8.6 – 11.0
Mean	9.43	9.6	9.5	10.4	10.1		9.79 ± 0.62

*Bracket numbers indicate number of observations.
†Numbers following mean are standard deviations.

would rise to higher levels, and within a week return to its former lower level.

The differences between mean serum inorganic phophate values for evaporated milk-fed infants and for breast-fed infants at each day of life were studied. These differences were found to be significant.[5] On the other hand, the differences between the phosphate values for artificial colostrum and breast milk, at any age, were not significant.

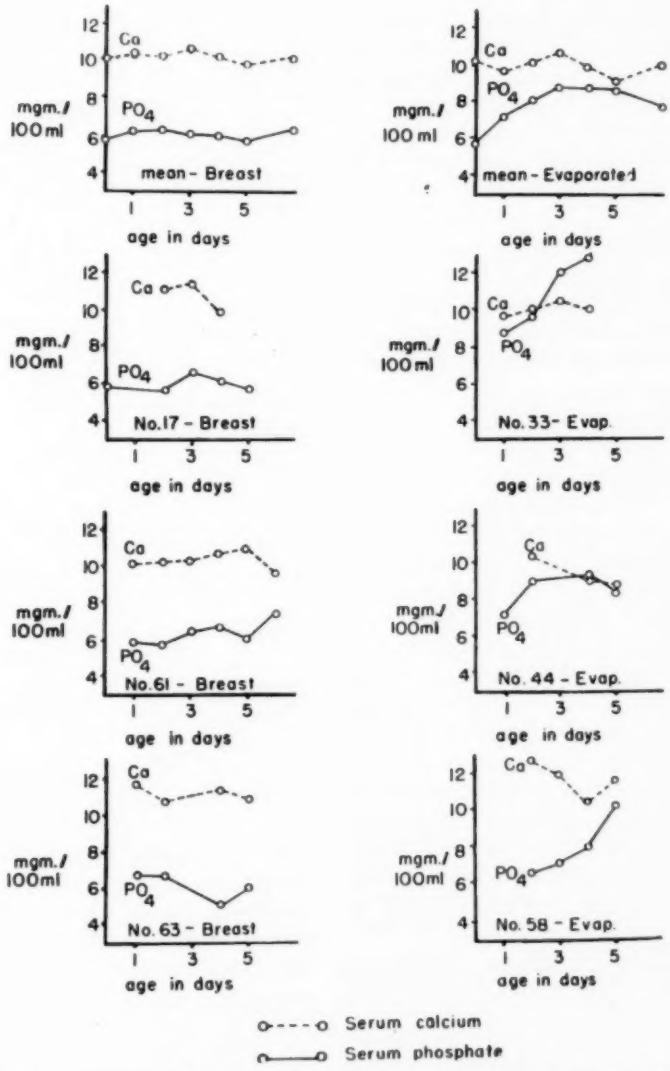

Fig. 1.—Serum calcium and inorganic phosphate plotted against the day of life. Mean values for breast and evaporated milk, and some individual examples.

In Table II are listed the serum calcium values as milligrams per 100 ml. of serum, also according to the feeding and age in days. Here, the values are all within a relatively narrow range (8.1 to 12.6 mg.). If we study the differences between the mean values for serum calcium for infants fed breast and evaporated milk, we find that at no time is there a significant difference, although on each day the serum calcium values of those infants fed evaporated milk are slightly lower. It may be noted that there is no constant correlation between the lower serum calcium values and the elevated serum phosphate levels. In Fig. 1, serum calcium and phosphate have been plotted against the age in days. The individual examples illustrate the variation to be found in infants on evaporated milk.

In order to determine the relationship between serum calcium and phosphate in these infants, two methods were used. First, for those samples on which both determinations were carried out, calcium was plotted against phosphate. The resulting graph presented such a wide scattering that the only valid observation possible was that most of the figures for breast, artificial colostrum, and breast plus artificial colostrum were to be found on the side of lower phosphate levels, while those for evaporated milk tended to be clustered around the higher levels. No striking differences were noted in the calcium values of the different groups.

The second method used to establish the degree of relationship between these two sets of values was the calculation of the coefficient of correlation "r" for these two variables, and its application to the regression equation.* "R" was calculated to be -0.1, and was applied to the regression equation:

$$\text{Calcium} - \text{mean calcium} = \frac{\text{"r" s.d. calcium}}{\text{s.d. phosphate}}$$

(phosphate – mean phosphate). Then: calcium – 10.07 = (0.1) $\frac{0.81}{1.33}$ (phosphate – 6.93).

From this it would seem that for each 1.0 mg. rise in serum phosphate there is a fall of 0.06 mg. in serum calcium. However, the standard error of our correlation coefficient, which is the reciprocal of the square root of the number of observations minus one, is 0.08, and we must conclude that this apparent inverse relation might very probably have occurred by chance in this number of observations.

Since it has been claimed that with high phosphate intake, in artificially fed infants, there is a hyperphosphatemia *and* hypocalcemia, it was decided to apply this same equation to the values for evaporated milk alone. This was done and a value for "r" of plus 0.1 was obtained indicating no significant relationship between blood phosphate and calcium in infants fed evaporated milk.

Several infants in this study, whose feedings were breast milk or artificial colostrum and maintained a relatively constant phosphate level for two weeks, were changed to a cow's milk preparation, and showed an appreciable rise in serum phosphate lasting a few days, soon returning to normal. For example, one infant in the series was kept on

*As given by Hill[5]:

$$\text{"r"} = \frac{\frac{\text{Sum of (phosphate} \times \text{calcium)}}{\text{no. of observations}} - (\text{mean phosphate} \times \text{mean Ca})}{\text{std. deviation of phosphate} \times \text{std. dev. of calcium}}$$

artificial colostrum for seventeen days and then changed to evaporated milk. On the second, third, fourth, fifth and seventeenth days his serum phosphates were, respectively, 6.3, 6.9, 7.0, 7.5, and 6.6 mg. per 100 ml., but on the twenty-first day, after four days on evaporated milk, it was 8.8 mg. Another infant was on artificial colostrum until the twelfth day and then changed to evaporated milk: at birth, and on the first, third, fourth, fifth, and twelfth days his serum phosphates were: 5.1, 5.4, 7.4, 7.2, 6.4, and 6.0 mg., but at 15 days it was 9.4, at 18 days 8.6, and on the twenty-first day it had fallen to 6.8 mg. per 100 ml.

DISCUSSION

In this study, those infants fed cow's milk had increases in serum phosphate, but this was not correlated with the serum calcium. Those infants fed breast milk had lower serum phosphates, but the serum calciums were similar. These differences were apparently due to the higher phosphate intake, as cow's milk has ten times the concentration of phosphate but five times the calcium content of breast milk.

Although the serum calcium values of those infants given cow's milk showed more variability than those given breast milk, no definite relationship could be established between the serum calcium and the serum phosphate.

Gardner[6] has recently re-emphasized Bakwin's*[7] hypothesis that high phosphate intake was accompanied by hypocalcemia, but Gardner also states that high phosphorus intake is not the only source of hypocalcemia and tetany, pointing out that these states occur in some breast-fed infants. Other factors, such as renal immaturity discussed by Snelling[8] and hypoparathyroidism, are obviously important in regulating the serum levels of calcium and phosphate.

In the infants in the present study, the phosphate-regulating mechanism has been seen to be remarkably well developed shortly after birth. Several of the infants studied were given breast milk and then a phosphate load in the form of cow's milk. Adaptation to this load was found to occur within six days, in the presence of continued elevation of phosphate intake.

Except for the greater variability found here of serum calcium and phosphorus of those infants fed cow's milk, it is very difficult to agree with the concept that high phosphate intakes, besides causing the evident hyperphosphatemia, do in any consistent way cause a hypocalcemia in the normal infant. Thus, of the factors which may cause hypocalcemia in the newborn infant, dietary factors are of only secondary importance.

SUMMARY

1. Seventy-nine infants given varied types of feeding were studied in the first few days of life with special reference to serum calcium and serum inorganic phosphate.

2. Higher phosphate values were found for infants on a cow's milk preparation than for infants who were breast fed.

3. The normal phosphate values of the breast-fed infants were very nearly

*Bakwin suggested in 1937 that the most likely cause of tetany in the newborn infant was a temporary hypoparathyroidism. Other factors he listed in its pathogenesis are: increased phosphate content of serum due to temporary neonatal starvation, decreased vitamin D stores, and increased phosphate in cow's milk.

duplicated with an artificial preparation closely approximating the composition of human colostrum.

4. No significant differences in the serum calcium for these infants could be shown.

5. This study confirms the many observations that the serum phosphate of newborn infants varies with the phosphate intake, but that normally high values are compensated for by the normal infant in a few days. This hyperphosphatemia, when it occurred, was not accompanied by a consistent hypocalcemia.

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THE USE OF BAL IN THE TREATMENT OF ACUTE LEAD ENCEPHALOPATHY

GARRETT E. DEANE, M.D., FREDERICK J. HELDRICH, JR., M.D., AND J. EDMUND BRADLEY, M.D.
BALTIMORE, MD.

THE use of BAL (2,3-dimercaptopropanol) has proved satisfactory in the treatment of certain heavy metal poisonings.[1] Recently, BAL has been used successfully in the clinical management of acute lead encephalopathy.[2, 3]

In this paper we have summarized the results of treatment in fifty-four cases of acute lead encephalopathy admitted to the University Hospital. The cases are divided into those treated before the advent of BAL and those treated with BAL. This division was made in an effort to evaluate the efficacy of BAL. Added information was tabulated in regard to incidence, symptomatology, and laboratory findings.

SELECTION OF CASES

Only those patients with a definite diagnosis of acute lead encephalopathy are admitted to the pediatric department of the University Hospital during the past two decades are included in this report.

CRITERIA FOR DIAGNOSIS

The criteria for diagnosis were as follows:

1. *History.*—A definite history of ingestion or inhalation of lead-containing substances. In each case an effort was made to determine the source of lead. It was found that thirty-two of the fifty-four patients had a documented history of eating lead paint and twelve patients of eating plaster. No history of lead ingestion or inhalation could be obtained in the remainder.

2. *Signs and Symptoms* (Table I).—These included convulsions, vomiting, and abnormal neurological findings. No correlation between lead level and degree of illness was found.

3. *X-ray Evidence.*—There were positive heavy metal lines at the metaphysis of the long bones on roentgen-ray examination. Forty-six patients had x-rays of their long bones, and of these, forty-one (89 per cent) had evidence of heavy metal deposition at the metaphyseal ends of their long bones.

4. *Blood Lead Level.*—A blood lead level of 0.06 mg. per cent or above was considered abnormal. Cases in this study revealed an average blood lead level of 0.25 mg. per cent, with a range of 0.08 to 0.73 mg. per 100 c.c. of blood.

5. *Urinary Coproporphyrin.*—A positive urine test for coproporphyrin of 2 plus or more. This test, which was described by Fischer and Duesberg,[4] has been found to give consistently elevated levels of coprophyrin in patients who subsequently proved to have elevated blood lead levels.

While it was not considered necessary to have a case satisfy all of the above diagnostic criteria to be included in this series, nevertheless the majority did, and all of the patients had blood

From the University of Maryland School of Medicine, University Hospital, Department of Pediatrics.

lead levels above the stated 0.06 mg. per cent.

METHOD OF TREATMENT

Hospital treatment prior to 1948 consisted of the use of calcium in the forms of lactate, gluconate, or chloride administered both orally and parenterally, and supplemented by high vitamin D intake, increased phosphorus intake, and sodium citrate.

After 1948 all patients were treated with BAL. A 10 per cent solution of BAL in benzyl benzoate and oil was used. The therapeutic regime was to give 3 mg. of BAL per kilogram every four hours for a total of ten days.

Supportive measures included in both series the use of barbiturates, intramuscular magnesium sulfate, and, in some instances, drop ether to control the convulsions. Fluid balance was maintained. Chemotherapeutic agents were used whenever infection was present.

As can be seen, the treatment in the two periods differed mainly in the addition of BAL to the exclusion of calcium and vitamin D.

Following hospitalization, those in the BAL-treated group were given daily oral sodium citrate. Kety and Letonoff[5] have shown that oral sodium citrate is followed by a fall in the concentration of lead in the blood and an increased urinary excretion of lead. These patients were also kept on oral sulfadiazine in an effort to prevent infection which was noted to be a frequent precipitating cause of acute lead encephalopathy. At monthly intervals after discharge these patients were followed in the outpatient department.

TABLE I. PRESENTING COMPLAINTS AND PHYSICAL FINDINGS IN CASES OF ACUTE LEAD ENCEPHALOPATHY

PRESENTING COMPLAINTS		PHYSICAL FINDINGS			
		Neurological Manifestations			
Vomiting	33	Eye signs	17→	(Strabismus, nystagmus, fundal pallor, pupil dilatation, etc.)	
		Convulsions	15		
Convulsions	22	Irritability	14	Stupor	6
Lethargy	13	Kernig	12	Hyperactive reflexes	4
Irritability	3	Coma	12	Cheyne Stokes resp.	2
Coma	2	Nuchal rigidity	8	Brudzinski	1
Headache	1	Babinski	7	Oppenheimer	1
Personalty changes	1	Hypoactive reflexes	7	Absent abdominals	1
		Lethargy	6		
		Manifestation of Infection			
Fever	4	Fever	23		
Cough	1	Tachycardia	18		
		Infection (upper respiratory infection)	13		
		General Manifestations			
Anorexia	7	Dyspnea	15		
Abdominal pain	5	Dehydration	12		
Constipation	4	Weight loss	7		
Weight loss	3	Lead line (gums)	4		
Epistaxis	1	Tender abdomen	1		

ANALYSIS OF FINDINGS

There were thirty-eight patients treated in the 1931 to 1948 group (Table II), and of these, ten died, while twenty-eight were discharged improved, a mortality rate of 26.31 per

cent. This over-all mortality in the pre-BAL group compares favorably with the results of McKhann and Vogt,[6] who found a mortality of 25 per cent, and Holt[7] of 65 per cent.

Sixteen patients were treated in the BAL group, only one of whom died, a mortality of 6.25 per cent. It should be pointed out here that those patients who died within twelve hours of admission are not included in either series, as it is probable that none of the forms of therapy would react favorably in those cases which entered with an overwhelming acute encephalopathy. The mortality of 6.25 per cent is considerably lower than the mortality reported by other workers. However, if these patients reported by Innes and Harrison who died during the first twelve to twenty-four hours after admission are omitted, their mortality rate becomes 12.5 per cent instead of 36 per cent—a figure which compares favorably with ours.

The patients in each group averaged 29.4 months in age with a range of from 15 to 84 months.

TABLE II. MORTALITY RATES PRIOR TO AND AFTER THE USE OF BAL IN ACUTE LEAD ENCEPHALOPATHY

PERIOD	PRE-BAL 1931-1948	BAL 1948-1951	TOTAL
Total number of patients	38	16	54
Total numbers improved	28	15	43
Total deaths	10	1	11
Mortality rate (%)	26.31%	6.25%	24.6%

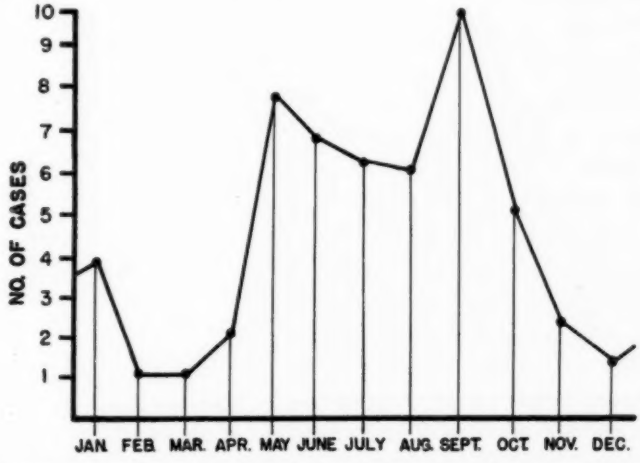

Fig. 1.—Illustrating that the usual peak incidence of acute lead encephalopathy is in the spring and summer months.

The average leukocyte count on admission was 16,310 with a range of from 5,000 to 27,000. Stippling of the erythrocytes was not a consistent finding. Spinal fluid changes showed an average pressure of 240 mm. H_2O with a range of from 50 to 380 mm. The protein averaged 113.8 per cent, and the leukocytes in the spinal fluid aver-

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aged 120. These results are similar to those of other investigators.[8]

The sex incidence was equal. Cases were found in all months of the year, but a peak incidence was noted in the spring and summer months (Fig. 1). Rapoport and Rubin[9] explain this same phenomena as being due to the antirachitic effect of solar radiation during this period resulting in an increase of lead adsorption from the intestine.

DISCUSSION

The treatment of lead poisoning in the past has been limited to the following three methods:

1. Those designed to limit the absorption of lead from the intestine, such as the administration of sodium or magnesium sulfate, which forms an insoluble lead sulfide in the lower intestine which is then passed in the stool, or gastric lavage.

2. Those designed to diminish the quantity of lead in the blood stream and tissues by facilitating its deposition and storage in the skeleton. This can be done through the administration of calcium and phosphorus, vitamin D, milk, and sodium citrate.[4]

3. Measures designed to affect gradual mobilization of lead deposits and elimination of the liberated lead from the body such as a low calcium, high phosphorus diet, parathyroid hormone, acids, acid-producing salts, alkali, and iodides.[8, 9]

It has been demonstrated that BAL is believed to act by displacing the metal from combination with sulfhydryl groups of proteins through the formation of a metal BAL complex. The heavy metal is thus kept in a nonionized and presumably nontoxic combination until excreted or stored in the body tissues in stable inert combination. There has also been evidence which indicates that administration of BAL will cause an increase in the urinary excretion of lead.[2] Though this urinary excretion of lead is temporary and does not continue as the drug is administered, this effect may help in reducing the blood lead level rapidly to a less toxic level.

Whatever the mechanism of action may be, it is suggested from the cases presented that further trials in the treatment of lead poisoning with BAL are indicated. It must be stressed, however, that supportive measures are of the utmost importance in the control and the prevention of acute lead encephalopathy. Of special importance is the control of infection and the resulting complicating acidosis which will tend to precipitate an attack of encephalopathy by mobilizing lead from its storage depots. It is our impression that too zealous administration of corrective parenteral fluids is to be avoided in cases of acute lead encephalopathy as it might increase cerebral edema.

SUMMARY AND CONCLUSIONS

A statistical survey of fifty-four cases of acute lead encephalopathy is presented. The patients are divided into two groups: those treated before BAL and those treated with BAL. The mortality rates were 26.31 and 6.25 per cent, respectively. A brief analysis of the clinical symptoms, signs, and laboratory data is presented. Stress is placed on the importance of supportive measures in the management of acute lead encephalopathy, especially the prevention of infection and acidosis. Because of the striking difference in the over-all mortality in the two

groups, further trials in the treatment of acute lead encephalopathy with BAL are indicated.

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ISOLATED MYOCARDITIS IN INFANTS

LIEUTENANT COLONEL GERALD J. CONLIN, JR.,* AND LIEUTENANT COLONEL FRANK A. MANTZ, JR.,** MEDICAL CORPS, UNITED STATES ARMY

"ISOLATED" myocarditis, first described by Fiedler[1] in 1899, has been discussed in American medical literature with increasing frequency over the past ten years. It is a nonspecific, idiopathic disease characterized clinically by progressive or sudden heart failure, frequently associated with various aberrations of the cardiac-conducting mechanism. The only constant structural changes are inflammation of variable type, confined exclusively to the myocardium, and cardiac hypertrophy for which no other cause can be demonstrated.

Boikan,[2] in attempting to classify Fiedler's myocarditis, described three types. The first is an acute diffuse lesion from which, he felt, recovery was possible. The second is a more chronic form which invariably causes death in a period of months. The third type is manifest by recent and remote cardiac changes which ultimately result in death from progressive heart failure.

The disease is seen most commonly in young adults and is not frequently recognized as a cause of death in infancy. We have found references[3] to only twenty-six proved or suspected cases occurring in babies up to 22 months of age. It is our purpose to record two additional instances of the disease in infants. In one of these, a clinical diagnosis was made and attempts at therapy were conducted.

From the Departments of Pediatrics, Gorgas Hospital, and Pathology, Board of Health Laboratory, Ancon, Canal Zone.

*Present address: OTSG, D/A, Washington 25, D. C.

**Present address: Percy Jones Army Hospital, Battle Creek, Mich.

CASE REPORTS

CASE 1.—A 14-day-old Negro male was admitted to Colon Hospital, Canal Zone, in a moribund state with short gasping respirations, extreme cutaneous pallor, and marked cyanosis of the lips and nails beds. Many crackling inspiratory râles were heard throughout the chest. The heart sounds were distant and the rate was 40 beats per minute. No murmurs were heard. He was given one ampule of Coramine and placed in an oxygen tent. In spite of artificial respiration, death occurred almost immediately.

The child was born in the hospital at full term by spontaneous, noninstrumental, somewhat precipitous delivery following a normal labor of six hours. The mother had been gravida i, para 0, and had experienced an uneventful pregnancy. Her past history was noncontributory. Serological tests for syphilis were negative and she was Rh positive. The father was alive and well but nothing further is known.

At birth, the cord was wrapped around the neck and the child was cyanotic. Slight difficulty was encountered in initiating respiration. Five minutes after spontaneous respirations were established, breathing became shallow and the child developed pallor and cyanosis. He responded well to physical stimulation and oxygen and no further difficulty was experienced.

From that time forward, the child remained well. Circumcision was ac-

complished without complication on the seventh day and he was vaccinated on the eighth day. Mother and child were discharged in good condition on the tenth day.

On the evening of the thirteenth day of life, the baby was irritable and cried frequently. During the following morning, the child vomited and did not take feedings well. At noon, he suddenly developed the gasping respirations and cyanosis which prompted hospital admission.

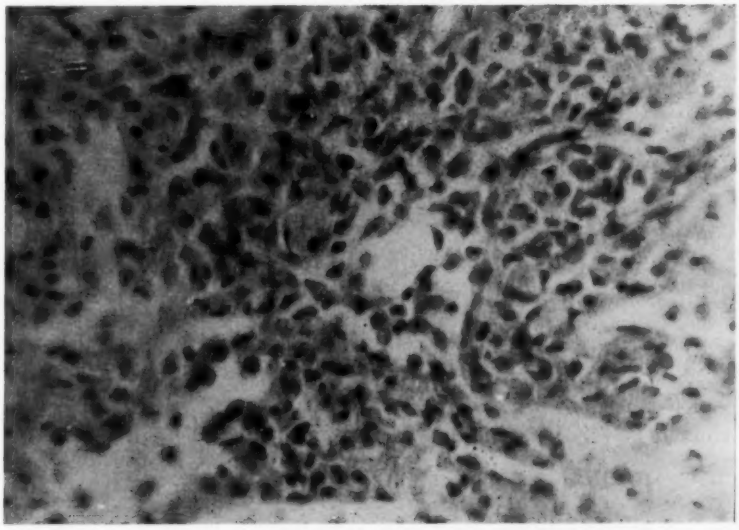

Fig. 1 (Case 1).—High-power magnification. Left ventricle. Intense infiltration of round cells among degenerating muscle fibers. Note mild concentration of inflammatory elements about dilated vessel.

Post-mortem Examination.—Autopsy was performed forty-two hours after death and revealed a well-developed, well-nourished, Negro infant weighing 10 pounds, and measuring 21 inches in crown-heel length. There was moderate cutaneous pallor and blue discoloration of the lips. A well-developed reaction of vaccinia was encountered over the left deltoid area. No further cutaneous lesions were seen.

The brain weighed 470 grams and was slightly edematous. A large thymus, weighing 20 grams, presented no abnormal features. No free fluid was found in the body cavities. The lungs were diffusely congested and edematous, the right weighing 56 grams and the left, 47 grams. Moderate mucosal hyperemia was noted in the lower trachea and larger bronchi.

The heart weighed 29 grams. It was globoid in outline with slight right-sided preponderance. The myocardium was firm, fleshy, and red-brown. No lesions were identified grossly. The right ventricle measured 4.0 mm., and the left ventricle, 5.0 mm. in thickness. Mild dilatation of the heart chambers was noted. The endocardium was unthickened, smooth, and unulcerated. There were no verrucae or adherent thrombi. No valvular lesions or congenital anomalies were seen. The coronary arteries were not remarkable. The ductus arteriosus was patent but empty and showed well-established obliterative endarteritic changes. There were no aberrations of the pulmonary or aortic conuses.

The liver weighed 160 grams and extended 3.0 cm. below the right costal margin. The spleen was slightly en-

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larged and weighed 16 grams. Both organs were deeply congested. The kidneys presented a combined weight of 28 grams and were similarly congested. Except for mild acute gastric dilatation, no other abnormalities were discovered. The lymph nodes were discrete, firm, and not enlarged.

Smears from the brain, spleen, bone marrow, and blood contained no parasites. No immediate or delayed sickling of erythrocytes was discovered. Serologic tests for syphilis on the blood and spinal fluid were negative. Cultures of heart's blood, ileum, colon, and spleen did not yield pathogenic organisms.

Microscopic Examinations.—It is unfortunate that heart disease was not suspected and only one segment from the left ventricle and left auricle was saved. Within the myocardium of the left ventricle was an intense and diffuse interstitial inflammatory reaction consisting of lymphocytes and mononuclear macrophages (Fig. 1). No polymorphonuclears or giant cells were seen. A definite predilection for perivascular distribution was noted. Marked myocardial degeneration was manifest chiefly by shrinkage and fragmentation of the fibers. Focal areas of myocardial necrosis were densely infiltrated with inflammatory elements, producing a slightly granulomatous appearance. Early fibroblastic proliferation was evident but no specific scarring was seen. The epicardium, endocardium, and the posterior leaflet of the mitral valve showed no abnormal features. Prolonged search under oil immersion failed to reveal inclusion bodies or parasites.

Except for intense passive congestion of the lungs, liver, spleen, and kidneys, there were no further significant lesions.

The cause of death was listed as acute isolated (Fiedler's) myocarditis with acute cardiac decompensation.

CASE 2.—A 52-week-old white female entered Gorgas Hospital, Canal Zone, with a chief complaint of fainting spells. The family history and prenatal history were noncontributory and the past history revealed only minor colds. The patient had been immunized against smallpox, diphtheria, tetanus, and pertussis. The present illness consisted of recurrent syncopal episodes beginning with a cry, followed by apnea and cyanosis. The first attack occurred at 2 months of age, the second at 8 months. During one episode she was seen by a physician who noted bradycardia and suspected heart block. This was confirmed by electrocardiogram. Three attacks occurred on the day of admission.

Physical examination revealed a well-developed, very irritable infant with a heart rate of 50, a soft systolic murmur in the fourth interspace left of the sternum, and mild miliaria.

Laboratory.—Hemoglobin was 82 per cent (Sahli); 4.43 million erythrocytes; 11,400 leukocytes with 66 per cent polymorphonuclear, 4 per cent eosinophils, and 30 per cent lymphocyte forms. Seven urinalyses, chest x-ray, feces examination, cellophane point perianal swab, and serologic tests for syphilis were negative. Tuberculin patch test (Vollmer) produced no reaction. Serum calcium was 9.3 mg. per 100 c.c., serum sodium 305 mg. per 100 c.c., serum potassium 20.4 mg. per 100 c.c. Complement-fixation test for antibodies against toxoplasma was negative.

Of the eleven electrocardiograms taken, all were abnormal. Portions of two of these are shown (Figs. 2 and 3). Disregarding minor differences of interpretation, readings 1, 4, 5, 7, and 10 showed definite two to one block, and nearly all demonstrated a greatly prolonged Q-T interval.

Course.—Medication with tincture of belladonna USP was begun and the dose was rapidly increased to a maximum of 10 drops every six hours. This was continued through the hospital course. At no time did the child show dilatation of pupils, flushing, dryness of mouth, or other observable indications of toxicity.

The temperature varied from 97° to 100.4° F.; no correlation was established between the temperature swing

and the medication. A clinical diagnosis of isolated myocarditis was made on the basis of the borderline fever, the mild leukocytosis, and the changing electrocardiograms for which no other explanation was apparent. A therapeutic trial with sulfadiazine was begun, on the eighteenth hospital day, using 5 grains (0.3 Gm.) every six hours, and 20 c.c. of 10 per cent sodium citrate solution for alkalinization of urine. No change in the clinical picture occurred except for twelve hours of unexplained fever to 103.4° F. on the ninth day of sulfadiazine. This therapy was discontinued after twelve days, and the following day the temperature rose to 102° F., at which time a common cold had developed.

On the thirty-second hospital day, a therapeutic trial of penicillin was begun, with dosage of 30,000 U. every three hours subcutaneously. Thereafter the highest temperature recorded was 99.0° F. and the patient seemed entirely healthy except for the bradycardia and soft systolic murmur. On the thirty-eighth hospital day while being bathed, she cried out, became flaccid, and respirations and heart tones ceased. Despite attempts at resuscitation, she died.

Postmortem Examination.—Autopsy, performed two and one-half hours after death, disclosed the warm body of a well-developed, well-nourished, white child weighing 23 pounds and measuring 31 inches in crown-heel length. There was a slight blue discoloration of the lips, oral mucous membrane, and nail beds. The cervical veins were distended and engorged with blood. No cutaneous lesions were seen.

Small amounts of thin, glairy, yellow, mucoid fluid were discovered within both internal ears which, on culture, yielded organisms of the genera Escherichia and Aerobacter. The membrana tympani were thickened, bilat-

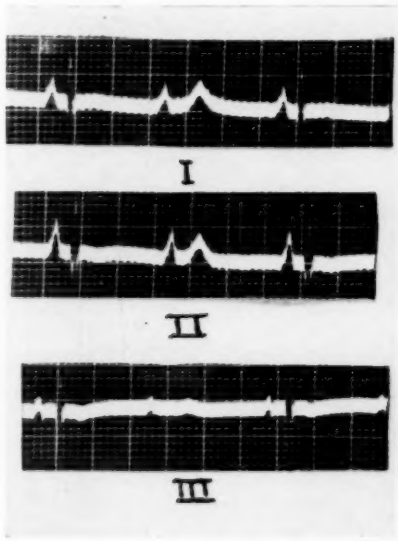

Fig. 2.

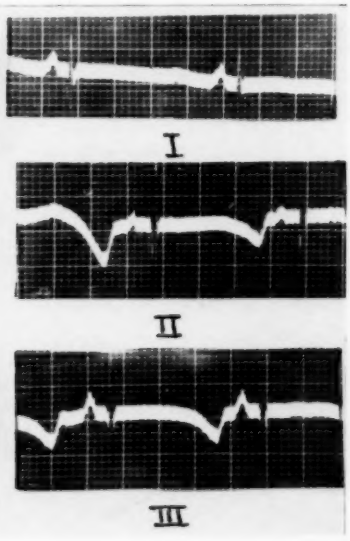

Fig. 3.

Fig. 2 (Case 2).—Electrocardiogram taken on nineteenth hospital day showing a two to one auriculoventricular heart block with small T wave only in Leads II and III.

Fig. 3 (Case 2).—Electrocardiogram taken on thirty-third hospital day showing extremely prolonged Q-T segment, inverted T_2 and T_3.

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erally, but there was no erosion of bone. The mucous membranes of the nose and accessory sinuses were yellow-tan, boggy, and bathed in scant amounts of watery exudate. The lymphoid tissue of the pharynx was moderately hypertrophoid.

The brain weighed 1,100 grams and was mildly hyperemic and edematous. The lungs presented a combined weight of 127 grams. They were edematous, hyperemic, and showed incomplete lobular atelectasis. Significant discrete enlargement of the tracheobronchial lymph nodes was apparent.

ulceration, verrucae, or adherent thrombi were demonstrated. There was mild dilatation of all valve rings, but no valvular lesions were found. The pulmonary conus was undilated, but the aortic conus was slightly widened. A small probe could be manipulated through the foramen ovale, but the septa were well formed and well apposed. The foramen was considered functionally closed, and no further defects were seen. The coronary arteries were well formed, patent, and not remarkable. A culture of heart's blood was sterile.

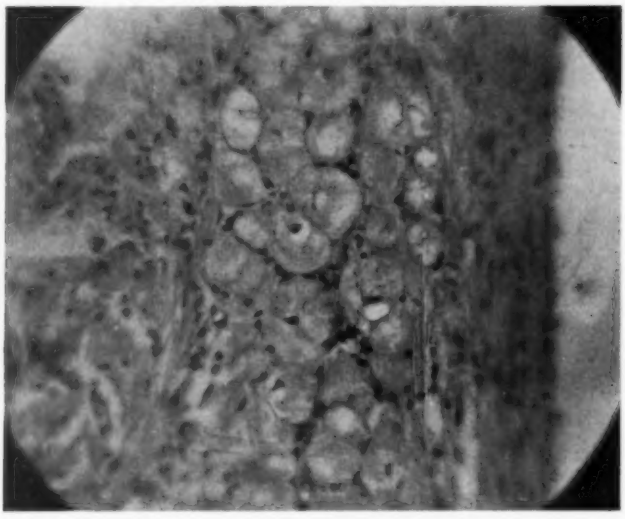

Fig. 4 (Case 2).—High-power magnification. Left ventricular side of interventricular septum. Marked hydropic degeneration and fragmentation of myocardial fibers with scant interstitial round-cell infiltration. Note similarity to changes found in beriberi.

The heart was markedly enlarged and globoid, having a cardiothoracic ratio of 8.0 to 12.0 cm., and weighing 75 grams. No pericardial lesions were discovered but 4 c.c. of straw yellow, watery fluid were contained within the sac. The myocardium was firm and gray-red with yellow-gray mottling within the papillary muscles of the left ventricle. There was mild ventricular hypertrophy and dilatation of all chambers. The right ventricle measured 4.0 mm. in thickness and the left ventricle 6.0 mm. The endocardium was thickened, opaque, and gray-white. No

Except for moderate hyperemia of the liver, spleen, and kidneys, the remainder of the gross examination was not abnormal.

Microscopic Examination.—A total of twenty-two sections of myocardium obtained from all heart chambers and septa were studied after staining with hematoxylin and eosin. The findings were not dramatic and significant lesions were discovered only after careful search. The most striking abnormality was swelling, hydropic degeneration, and fragmentation of the myocardial fibers particularly in areas un-

derlying the endocardium (Fig. 4). Fragmentation and degeneration of lesser intensity were apparent throughout, but nuclear degeneration was not prominent. The interstices were widened and hypercellular. Proliferating fibroblasts and Anitschkow's myocytes were present in increased numbers, but none of the atypical cell forms described by Marcuse[4] were discovered. Vascular dilatation, mild mural thickening, and perivascular

Fig. 5.

Fig. 6.

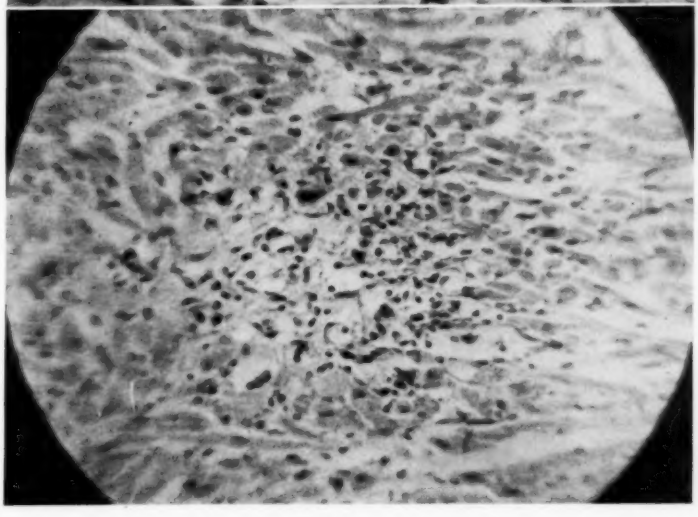

Fig. 5 (Case 2).—High-power magnification. Papillary muscle of left ventricle. Small perivascular accumulation of lymphocytes.

Fig. 6 (Case 2).—High-power magnification. Right ventricle. Focal necrosis in heart muscle.

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edema were apparent within the myocardium. No collagenized scars were found. There was a mild, diffuse, interstitial infiltration of lymphocytes found in greatest concentration about the blood vessels where they occasionally formed tiny inflammatory nodules (Fig. 5). Eosinophils and macrophages were encountered with lesser frequency, and no polymorphonuclear neutrophils were discovered. Prolonged search yielded rare focal sub-

Fig. 7.

Fig. 8.

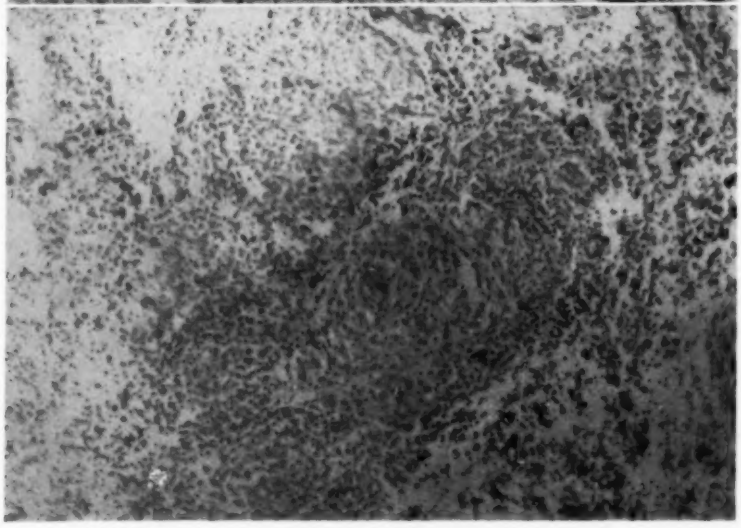

Fig. 7 (Case 2).—Low-power magnification. Left auricle. Lymphocytic infiltration at interface of myocardium and endocardium.

Fig. 8 (Case 2).—Low-power magnification. Peritracheal lymph node. Sarcoidlike nodules of epithelioid, reticuloendothelial cells.

miliary necrotic lesions within the myocardium. These were rather heavily infiltrated with lymphocytes and macrophages obviously removing destroyed muscle cells (Fig. 6). No caseation necrosis or giant cells were seen. The epicardium was uninflamed and free of exudate. Mild fibrous thickening of the endocardium and heart valves was apparent, but there were no ulcerations or verrucae. At the endocardial interface within the left interauricular septum, there was one small accumulation of lymphocytes representing the only significant endocardial lesion present (Fig. 7). No Aschoff's bodies or parasites could be found. In general, it may be stated that the lesions were widespread throughout the entire myocardium but showed a definite predilection for the intimal aspects.

The tracheal mucous membrane was thickened, edematous, and heavily infiltrated with lymphocytes, plasma cells, and polymorphonuclear leukocytes. No ulceration or membrane formation had occurred and the inflammatory reaction extended downward into the smaller bronchi.

There was diffuse reticuloendothelial hyperplasia of the thoracic and abdominal lymph nodes and of the spleen. A lymph node at the bifurcation of the trachea yielded lesions of particular interest. Here were tuberculoid nodules of epithelioid macrophages showing no necrosis or surrounding inflammatory reaction (Fig. 8). No giant cells or asteroid bodies were found, and no acid-fast organisms could be demonstrated. The lesions showed striking resemblance to sarcoid.

The remainder of the microscopic study merely confirmed the presence of moderately acute passive congestion and edema of the lungs, lobular pulmonary atelectasis, and acute passive congestion of the parenchymatous organs.

The cause of death was ascribed to acute, diffuse, "isolated" (Fiedler's) myocarditis, and the anatomic diagnoses included mild chronic serous otitis media, chronic pansinusitis, chronic tracheobronchitis, sarcoidlike lesions in a mediastinal lymph node, and acute passive congestion of vital organs.

DISCUSSION

The lesions discovered at autopsy fulfill admirably the oft-quoted dictums of Saphir[5] as to the requirements for the diagnosis. A diffuse myocarditis existed in two patients in whom the known causes for such lesions were absent, and the myocardial involvement was unassociated with major lesions in the endocardium, pericardium, or the entire body.

Our first patient presented an acute, diffuse, myocardial lesion which seems to correspond to the first type described by Boikan.[2] It is difficult, however, to conceive of recovery in a heart so intensely inflamed.

It seems appropriate to classify the disease found in our second patient with Boikan's second group. The lesions were most conspicuous within the inner half of the ventricular wall, the initial change was an infiltration of lymphocytes, and there was marked vascular dilatation. The older lesions were associated with myocardial necrosis and granulomatous inflammation, and there was evidence of early myocardial fibrosis. All these features are clearly described by Boikan.

The dearth of lesions and absence of dramatic changes were at first surprising in a patient with such marked electrocardiographic abnormalities. This, however, is a well-recognized feature in certain cases of isolated myocarditis and has been discussed by Saphir[6] and by Helwig and Wilhelmy.[7] The latter authors laid great stress upon myocardial degeneration and fragmentation as an important pathologic diagnostic feature.

The extreme hydropic degeneration of certain myocardial fibers encountered in our second case are similar to those described by Wenckebach[8] in the

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beriberi heart. This feature has been used by Smith and Furth[9] in three cases, and by Toreson[10] in one case, to imply relationship to deficiency disease. Our patient, however, yielded no historic or morphologic data which might be so construed.

The sarcoidlike lesions within the mediastinal lymph node are exciting and possibly significant findings. A chronic granulomatous form of isolated myocarditis is discussed by Saphir[5] and probably corresponds to the third type of Boikan. Miller[11] has described one case under the term "granulomatous myocarditis" and, more recently, Kean and Hoekenga,[12] from this laboratory, have reported two cases of atypical myocardial inflammatory disease under the term "giant-cell myocarditis." In one of the latter two cases, noncaseous tuberculoid lymph node lesions were found. It seems entirely conceivable that a relationship exists. Fiedler's myocarditis may well be a chronic progressive disease, ending in granulomatous inflammation in patients who survive long periods, and the reticuloendothelial system may be involved in some way. A direct relationship to sarcoidosis is not implied in this paper.

Of other associated lesions, both our patients had large thymus glands, a finding unusual in acute infections or wasting diseases. Of five juvenile cases described by Saphir[5] each had a large thymus. No conclusions can be drawn from this feature.

Saphir[5] has called attention to upper respiratory inflammation in isolated myocarditis. It is noteworthy that both cases herein described presented evidence of mild tracheobronchitis. Diphtheria, a prominent cause of myocarditis, was ruled out in both instances by gross and microscopic examination and by bacteriologic studies in Case 2.

A possible relationship to virus infection is suggested in Case 1 because of the concurrent vaccination "take." Helwig and Schmidt[13] have isolated a virus from anthropoid apes dying of interstitial myocarditis, but no apparent relationship to the virus of vaccinia exists. There is little evidence thus far that the agent of ape myocarditis is pathogenic for man. A prolonged search of heart sections failed to reveal the presence of inclusion bodies in this instance.

Myocarditis and degeneration of the renal tubules has been produced experimentally by Follis[14] in rats deprived of potassium. In both our cases the nutritional intake was excellent and no renal lesions were demonstrated. A single blood potassium determination in the clinical examination of Case 2 was within normal limits.

Although Aschoff's bodies could not be found in either case, the possibility of rheumatic fever cannot be eliminated absolutely. This is the opinion of most authors who have studied isolated myocarditis at autopsy. Raeburn[3h] in commenting on the essentially interstitial and perivascular nature of the inflammatory process, suggested a similarity to the collagen system diseases. He implied a possible relationship to polyarteritis nodosa based upon the perivascular concentration of inflammatory cells. This interesting concept seems worthy of further consideration.

It is felt that influenza, diphtheria, pneumonia, parasitic disease, the specific granulomas, hyperthyroidism, beriberi, burns, allergy, and other accepted causes of myocarditis can be excluded in our cases.

SUMMARY

1. Two cases of isolated (Fiedler's) myocarditis in infants are recorded.

2. A clinical diagnosis was established in the second case on the basis of bradycardia, low-grade fever, syncope, and changing electrocardiograms for which no other apparent cause could be discovered.

3. Although the fever was altered by penicillin, no therapeutic responses were elicited by sulfadiazine or atropine in high dosage, and these agents failed to prevent syncope and death.

4. The pathology and etiology of isolated myocarditis are discussed briefly. It is postulated that isolated myocarditis is a chronic progressive disease ending in granulomatous inflammation in patients who survive long periods.

5. Isolated myocarditis should be considered in the differential diagnosis of cryptogenic cardiac arrythmias and cardiac enlargement occurring in infants.

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CHANGES IN BLOOD COAGULATION FACTORS DURING THE FIRST WEEK OF LIFE

CHARLES A. OWEN, JR., M.D., AND MARGARET M. HURN, M.S.*
ROCHESTER, MINN.

THE nature of the clotting defect in hemorrhagic disease of the newborn infant is still imperfectly understood. In 1937, Brinkhous and associates[1] reported that the concentration of prothrombin in blood of newborn infants was only about a fourth that of adults; in infants who had hemorrhagic disease the value was even less. However, simple hypoprothrombinemia does not appear to explain completely the phenomenon of this hemorrhagic disease, for these investigators noted that the deficiency in prothrombin of normal infants was corrected slowly during a period of several months, whereas neonatal bleeding usually is manifested only during the first few days of life.

In 1939, it was found[2, 3] that so-called prothrombin time, as determined by the Quick test for plasmatic clotting time, was prolonged during the first week of life, which more closely coincided with the period of susceptibility to hemorrhagic disease. The classic work of Waddell and coworkers[4] on the treatment of this disease with vitamin K is well known.

In 1949, Randall and Randall[5] reported that when the plasma of infants, which had a long prothrombin time, was mixed with aged (adult) plasma, which also had a long prothrombin time, the prothrombin time of the mixture was shortened significantly. Thus, aged plasma, known to lack labile factor[6] (Ac-globulin[7] or accelerin[8]), appeared to contain something that was lacking in infant plasma; in turn, infant plasma probably contained the labile factor that was missing in aged plasma. It might be suspected that aged plasma furnished prothrombin, since infant plasma is known to be wanting in that substance. However, the Randalls found that serum, which is virtually free of prothrombin, also exerted a corrective influence on the prothrombin time of infant plasma.

In recent years a stable factor[9] present in serum has been proposed as important in blood clotting; terms which probably are synonymous with "stable factor" include "cothromboplastin,"[10] "convertin,"[11] "factor VII,"[12] and "S.P.C.A."[13] Loeliger and Koller[14] assayed this new factor in blood from the umbilical cord of newborn infants and found it to be uniformly depressed. This evidence might be interpreted to indicate that the deficiency found by the Randalls is in fact a lack of stable factor. However, no studies have been presented to elucidate the mechanism of the spontaneous return to normal of the prothrombin times of newborn infants after the first few days of life or of the more rapid recovery induced by administration of vitamin K.

From the Section of Clinical Pathology, Mayo Clinic.
*Research assistant.

METHODS

Normal, full-term infants, born during the summer, were studied in two groups: each baby in one group received while still in the delivery room 2.5 mg. of menadione sodium bisulfite (Hykinone), an analogue of vitamin K; the other group received none. For the most part breast feedings were supplemented on the third day with formulas incorporating evaporated milk. Samples of blood were obtained from antecubital or femoral veins.

The two-stage test of Warner and associates[15] was used, with slight modifications,[9] for evaluation of the concentration of prothrombin in plasma. The one-stage test of Quick was performed as adapted to its routine use at the Mayo Clinic.[16] Cothromboplastin was assayed by the technique of Mann.[17]

Labile Factor.—Aged plasma was prepared when adult human oxalated plasma was left at 5° C. until the prothrombin time exceeded 60 seconds. Small aliquots of the plasma were then frozen. To 9 parts of this plasma, which was deficient in labile factor, was added 1 part of infant plasma. The prothrombin time of the mixture was compared with that of mixture of 9 parts of aged plasma with 1 part of normal adult plasma.

Stable Factor.—Plasma was obtained from dicumarolized patients. To 9 parts of this plasma, which was deficient in stable factor, was added 1 part of infant plasma. The prothrombin time of this mixture was compared with that of a mixture of 1 part of normal adult plasma with 9 parts of dicumarol plasma. The dicumarol plasmas contained prothrombin in the same range of concentrations as did the infant plasmas; changes in prothrombin times of mixtures of these two types of plasma cannot be attributed to changes in the concentration of prothrombin. Values designated as per cents in all the one-stage clotting systems used in this investigation are based on a comparison of the observed prothrombin times with standard curves obtained by serial dilution of normal plasma with isotonic solution of sodium chloride.

RESULTS

Quick Test.—The findings in Table I agree with those recorded in the literature. A lengthening of the prothrombin times (reduced "prothrombin activity") was noted in the first few days of life; the prothrombin times shortened spontaneously after the third day. The prothrombin times of the babies who received vitamin K at birth tended to remain normal.

Concentration of Prothrombin.—The results (Table I) again agree well with those in published reports; even in the babies who received vitamin K the values for prothrombin were less than half of adult values. In this limited series, the concentration of prothrombin did appear to be somewhat less in the younger infants who received no parenteral vitamin K; this was particularly evident in infant 6 (Table I) who, however, exhibited no hemorrhagic tendency.

Labile Factor.—Teng[18] has reported normal concentrations of Ac-globulin in normal infants. Similarly we found that in only one of the twenty-two samples of blood tested (Table I) did the plasma of an infant correct the deficiency of aged plasma less efficiently than did normal adult plasma, and in that instance the difference was

slight. In fact, the plasma of the infants often could be diluted several-fold and still be as effective as undiluted adult plasma. This suggests that the amount of labile factor in the plasma of infants may be considerably more than that in adults, a condition simulating that of a number of animals which have greater ratios of labile factor to prothrombin than does man.

assay of cothromboplastin were consistently lower than those obtained by correction of the clotting defect of dicumarol plasma, the trends were clearly similar.

COMMENT

The mechanism of blood coagulation in infants during the first few months of life apparently differs from that in adults. Despite the presence of normal clotting times for whole blood, infants exhibit a degree of hypoprothrombinemia that would be considered serious in an adult. In addition, during the first week of life, a potential bleeding tendency appears; this is associated with prolongation of the clotting times of whole blood and of plasma, as measured by the Quick test,[3] and a reduction in the amount of stable conversion factor. All these

TABLE I. CONCENTRATION OF COAGULATION FACTORS IN PLASMA OF NEWBORN INFANTS

INFANT	AGE (HR.)	PER CENT*				
		QUICK TEST ("PROTHROMBIN ACTIVITY")	TWO-STAGE PROTHROMBIN TEST	LABILE FACTOR	STABLE FACTOR	COTHROMBOPLASTIN
1	34	30	28	100	25	20
2	35	19	17	100	10	8
3	35	8	25	100	<10	5
4	37	20	16	100	30	13
5	41	31	24	100	20	16
6	44	7	9	100	<10	5
7	48	40	34	100	30	25
8	53	15	15	100	10	10
4	61	35	21	100	40	25
1	82	60	32	100	50	35
2	83	50	29	100	40	15
5	89	60	22	100	50	25
9	122	70	36	100	50	35
Received menadione sodium bisulfite						
10	40	45	16	85	40	30
11	62	100	42	100	80	45
12	69	100	34	100	100	50
13	96	100	37	100	80	72
14	103	75	45	100	70	55
15	115	100	36	100	80	65
16	119	100	47	100	100	82
17	134	75	35	100	60	50
18	173	100	39	100	90	70

*Per cent of normal adult values.

Stable Factor.—The stable factor was found to be depressed during the period of prolonged prothrombin times (Table I). This confirms the results reported by Loeliger and his associates and by the Randalls. However, during the spontaneous period of recovery the concentration of stable factor increased; when vitamin K was administered, the amount of stable factor increased almost to normal adult values. While the values determined by the

changes are superimposed on the existing hypoprothrombinemia. Except for the reduced titer of prothrombin, these alterations may be prevented by the administration of vitamin K.

Just why these neonatal changes in clotting should occur is not clear. The transient lengthening of plasmatic clotting times (Quick test), reflecting a deficiency of stable factor, seems related to an insufficiency of vitamin K, for it has been demonstrated that administration of minute amounts of this vitamin can correct or prevent the clotting abnormality.[19] The true hypoprothrombinemia, not at all apparent from values for the Quick test, continues for several months; it may be related to the functional capacity of the liver, for certain reports[20, 21] note a comparable inability of the infant to dispose of intravenously administered sulfobromophthalein.

The behavior of the Quick test during infancy is inexplicable if it is assumed to be a measure solely of prothrombin. It has been suggested that this test, rather than an actual measurement of prothrombin, is more concerned with the ability of prothrombin to convert into thrombin, and thus is limited by the concentration of the labile and stable conversion factors.[9, 22] The evidence presented here would tend to support this claim, for the concentration of prothrombin varied only moderately while the concentration of the stable factor fluctuated widely and in parallel with the values for the Quick test.

SUMMARY

Various factors concerned with the clotting of blood were studied in normal, full-term infants during their first week of life.

During the period when so-called prothrombin times (plasmatic clotting times determined by the Quick test) were lengthened, infant blood was deficient in both prothrombin and stable factor, but not in labile factor.

When an analogue of vitamin K was administered at birth, the infants' prothrombin times tended to remain normal, the concentration of prothrombin was still diminished, the concentration of the stable factor approached adult values and the amount of labile factor continued to be normal or was more than adult values.

Variations in the blood clotting of infants during the first week of life, as measured by the Quick test, appeared to parallel the concentration of the stable factor. This is in agreement with the concept that the Quick test is primarily an index of the accessory conversion factors and not of prothrombin.

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TEACHING INFANTS TO WALK: PHYSIOLOGICAL CONSIDERATIONS

MAURICE H. HERZMARK, M.D.
WASHINGTON, D. C.

PEDIATRICIANS and parents are ever more alert in finding skeletal defects in infants. Calcaneovalgus which was seldom noticed until the child began to walk is now noted soon after birth and treatment is started early. But weaknesses and distortions which result from unphysiological use of the feet may take years to become symptomatic or very noticeable, and attempts at correction during infancy are not as frequent as during adolescence.

The period when a child begins to take his first steps is a very critical one, for habits of standing and walking acquired at this time may last throughout life. These habits may make the difference between unlimited activities and opportunities, or limitations due to weak, pronated, painful feet.

The human foot has been adapted over thousands of years to walking easily and swiftly over rough, irregular ground. The arrangement of the bones and muscles is such that several arches develop to reduce the contact between the foot and the walking surface to a minimum. This permits standing and walking over pebbles and stones, twigs and clods, or rocks and crannies with little discomfort. The ambulatory style of our early American Indians has become a model for proper walking, and their graceful intoeing gait is emulated by our athletes and professional walkers. Their foot development was simply the normal physiological response to their terrain. Their babies did not have smooth, paved surfaces to play on. Their nursery floors were pebble-strewn paths, stony crags, and clod-covered meadows (Fig. 1). Following a design millions of years old, their feet responded to the stimulus of Mother Earth's carpet and adapted themselves to the demands put upon them.

Our urban infants usually learn to walk on flat, smooth surfaces—the nursery floor paved with linoleum, the play pen with a smooth plywood bottom, or the polished rug-covered floor of the bedroom. When the baby first stands, his legs are weak, so to steady himself, he separates his feet and turns them out to get as broad a base as possible. This throws the weight on the longitudinal arches, everts the heels, and thrusts the heads of the astragali medially (Fig. 2). Since there is nothing underfoot to stimulate the intrinsic muscles of the feet, or make this position uncomfortable, this unphysiological stance and gait may become a habit very difficult to overcome when it becomes a source of disability in later life.

The inordinate number of young adults with weak painful feet, unable to meet the demands of military training, proved a great handicap during the recent wars. The majority of these

Address: 1612 Rhode Island Ave., N. W.

men came from urban areas. The military medical facilities tried all the usual remedies such as arch supports of all kinds, modified shoes and specially made shoes, exercises, and such, with discouraging results. Large numbers of soldiers had to be relieved of service when they were sorely needed, with a medical discharge, the diagnosis reading "Pes planus, symptomatic."

Fig. 1.—Primitive Indian baby standing barefoot on pebble-strewn ground in front of tepee. Note that although feet are separated, they are not pronated.

Fig. 2.—Note the marked pronation of the right foot on a flat surface even though carpeted.

Impressed by the excellent feet of primitive peoples seen during military service, I started some observations on our infants just learning to walk. Feeling certain that flat feet were caused by a flat surface, and normal feet developed on an irregular surface, a pad for the play pen was constructed to simulate the ground. On the basis of many measurements, the pad was made of sponge rubber, the surface studded with knobs ¼ inch high with a base of 1¼ inches in diameter and separated in staggered arrangement ⅝ inch apart. Nowhere was there a flat surface large enough to support a foot, and the size and arrangement of the knobs were such as to engage the hollow longitudinal arch as the infant walked over the surface. This type of pad was tried out in the play-pens of a number of infants learning to walk, and on many that had learned to walk with a pronated gait. It was seen that when the foot came in con-

tact with the knobs, the toes made reflex grasping movements (Fig. 3), and since the knobs engaged the longitudinal arch, the foot could not pronate, but tended to go into inversion. Those infants who had developed a tendency to walk in pronation found themselves unable to do so on the knob-studded surface, since a flat surface is needed for such a gait.

Fig. 3.—Note how the toes make reflex grasping movements on irregular knob-studded pad.

Since 1947 when the pad was first described,[1] a number of infants have been taught to walk on this specially designed, irregularly surfaced pad, and the results have been very encouraging. A number of pediatrists have tried the pad on their own babies and reported very satisfactory results. Although more observations are being made, and different types of materials are being tried out, the basic design of the pad has been found satisfactory. It is my firm conviction that children taught to walk on an irregular springy surface will develop the intrinsic muscles of their feet and legs as do the offspring of primitive peoples who have no paved surfaces to flatten their feet. Physicians aware of the physiology of the human foot should make use of the principles of natural adaptation, to prevent the alarming increase of so painful and disabling a foot condition as pes planus.

The most favorable time to teach a child proper habits of standing and walking is when he first takes the erect posture, and during this time keep his feet away from flat, hard surfaces.

Teaching baby to walk on an irregular resilient surface instead of a flat, hard surface has been found to be an excellent method of developing proper habits of standing and walking. Flat, pronated feet are weak feet, and the great majority of infants, given an opportunity to develop their foot and leg muscles according to physiological principles, will respond by growing up with strong, well-balanced feet.

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DUODENAL ATRESIA

WILLIAM C. BECK, M.D., AND GEORGE CHOHANY, M.D.
SAYRE, PA.

IN RECENT years there appears to be a slightly increasing number of cases of duodenal atresia reported in the literature. From the time of the first successful operation reported by Ernst[1] in 1916 until the report of Benson and Penberthy[2] in 1948, approximately thirty cases had been reported. Since the latter's report of two successes, several others have been reported. Now about forty patients are alive and well following operative intervention. The anomaly is rare and frequently delayed in diagnosis. The operative mortality is high. This is emphasized by the fact that Ladd and Gross[3] report saving only one of five patients.

INCIDENCE

It is difficult to estimate the incidence of duodenal atresia. Benson and Penberthy state that it occurs about once in each 20,000 births. Davis and Poynter[4] quote Miller who, in 1894, found thirty-six cases of intestinal atresia and stenosis in 65,000 autopsies on children. As this includes all types of atresia and stenosis as well as imperforate anus, one may conclude that the former figure may well be correct. With about 3,500,000 births in the United States each year, this would mean that about 175 cases should be found. Granted that only a part of the successful cases are reported, one may still conclude that only a very small number of these patients are recognized and treated.

From the Surgical Service of the Guthrie Clinic and Robert Packer Hospital.

The site of intestinal atresia may be at any level. Miller and his associates[5] found that they occur most frequently at one of four sites: (1) the esophagus at the level of the bifurcation of the trachea, (2) the duodenum close to the ampulla of Vater, (3) the lower portion of the ileum at the level of the omphalomesenteric duct, and (4) the lower part of the rectum and anal canal. They quote Bland Sutton who, more than sixty years ago, said that atresias are most likely to be found in those places where the embryologic processes are most complex, and the chances of error in development are the greatest. White and Collins[6] suggest that there is a relationship between the site of the atresia and the embryonic blood supply, i.e., where the foregut and the midgut join. This would hold true for the duodenal atresias, but not for the junction of the mid- and hindgut.

Davis and Poynter found that intestinal atresias occur in approximately one-third of all of the congenital atretic bowels. They think, however, that the four to one preponderance of imperforate anus to all other intestinal atresias reported in the literature is due to diagnostic discrepancy rather than actual incidence.

ETIOLOGY AND ANATOMY

It appears to be generally accepted that during a certain phase of embryonal development, the intestines consist in a solid cord. Later the central cells disintegrate to form large vacu-

oles which coalesce so that the intestinal tract becomes tubular. If such coalescence is incomplete, a variety of atresia, stenosis, or septum will result.

Three sites of atresia are observed: (1) the obstruction is proximal to the ampulla of Vater, (2) the obstruction is distal to the ampulla, and (3) the septum also involves the ampulla with a secondary obstruction of the biliary tract. Of these three, the second is the most frequently encountered.

Although there have been descriptions of both a diaphragm and of a narrowing down to a pin-point opening, as well as an area of a closed solid cord in the infant, these types merge from one to the other. Diagrammatic representation of the type of the atresia is of academic interest only, and, in our experience, is most difficult even at necropsy. It suffices to know that the continuity of the bowel is either partially or completely broken.

CLINICAL PICTURE AND DIAGNOSIS

Duodenal atresia results in a high intestinal obstruction. As we have pointed out in a previous publication on duodenal obstruction[8] in the adult, the only consistent symptom is vomiting. Ladd and Gross observed that these babies always have symptoms on the first day of life. Vomiting occurs during or after nursing and becomes progressively more frequent and intense, even projectile. As almost all of the obstructions are below the ampulla, the vomitus usually contains bile. In the rare instances of accompanying biliary atresia, the vomitus will not contain bile and the baby will be jaundiced. This is not, however, too prominent an early symptom, as is evidenced by the cases of pure biliary obstruction that we have seen. We have seen a week lapse before the skin and sclera were deeply stained. Neither does jaundice mean that the biliary tract is involved. One of our cases reported herein was jaundiced.

The stool may be of some help in establishing the diagnosis, but this is surprisingly not too often the case. The meconium in the first day or two may appear almost normal. Farber[7] has demonstrated that in intestinal atresia there is no vernix caseosa in the stool. This material contains the desquamated epithelial cells from the baby's skin and is swallowed by the baby in utero. Therefore, the absence of cornified epithelial cells in the stool (Farber's test) is presumptive evidence that an intestinal obstruction exists.

Abdominal distention may or may not be present. It has not been observed in our cases. This symptom also appears to be uncommon in the other cases reported in the literature. It has been said that when it does occur, the distention is most severe in the upper abdomen. Fever has also been observed, as well as leukocytosis.

The other symptoms are those related to the physiological changes observed as a result of vomiting. Dehydration is soon observed as well as hypoproteinemia and hypopotassemia.

The diagnosis is suspected in any child who vomits on the first and second days of life. The investigation must be started immediately if a successful outcome is to take place. The diagnosis is established by roentgenographic examination. The abdominal scout film may, in itself, be almost diagnostic. The stomach contains gas, and the gas may be observed to be in two segments (Fig. 1). The second segment represents gas in the duode-

num. We have, in a previous communication,[8] shown that this may be even more dramatic in the lateral film, as the duodenum lies on a different anteroposterior plane from the stomach. The rest of the abdomen is singularly free of gas.

The roentgen examination then is continued after a No. 16 French urethral catheter has been introduced into the stomach. Under fluoroscopy, an iodized oil or aqueous radiopaque solution is introduced into the catheter. In our opinion barium should never be used, because of the danger of vomiting and aspiration. Silverman and Caffey,[9] however, find no contraindication to the use of a thin mixture of barium and have used it in a large series of patients. We see no advantage to barium other than an economic one, and the amount of the iodized oil used is not great. The picture (Fig. 2) is a typical one with the radiopacity outlining the stomach and the tremendously enlarged duodenum. This is sufficient to establish a diagnosis of duodenal obstruction. The diagnosis of its intrinsic or extrinsic nature is made at the operating table.

TREATMENT

Although the definitive treatment is surgical, the preoperative and postoperative care will determine the success or the failure of the intervention. Sufficient delay in the operation to secure a maximum of physiologic equilibrium is possible if the diagnosis has been made sufficiently early. During the preoperative care, vomiting should be stopped by repeated gastric aspiration. Fluid and electrolyte replacement should be in the hands of a com-

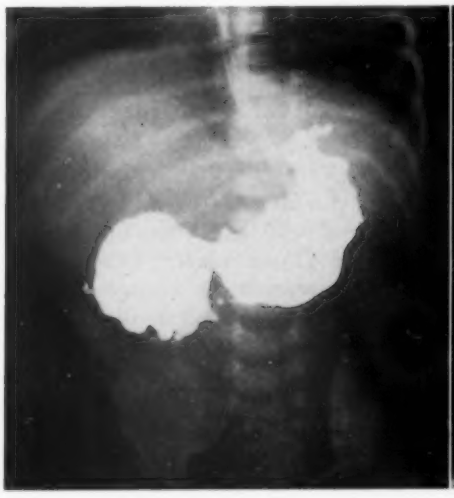

Fig. 1.

Fig. 2.

Fig. 1.—Preoperative x-ray film of Lipiodol study. Note the absence of gas in the small bowel and the tremendous dilatation of the first portion of the duodenum.

Fig. 2.—Postoperative film taken at 10 days of age. Note the gas-filled small bowel. There is still some dilatation of the duodenal bulb. The anastomosis shows quite clearly. This film was taken within a few minutes of a barium swallow.

petent pediatrician. Correction of the protein lack is probably as important a single factor in the favorable outcome. The hypopotassemia must be most carefully controlled. These children rapidly reflect all of the aberrations of their chemical balance, but they also respond remarkably quickly when the deficits are corrected.

Preparatively, it is important to have access to the vascular system so that we feel a catheter in a vein is imperative. The baby is brought to the operating room under oxygen, and transferred to the operating table with a high oxygen anesthetic started immediately. Our anesthetist prefers the use of rectal Pentothal and closed ether or often intubation for this surgery, complemented by the addition of local infiltration of the abdominal wall with one-fourth per cent procaine.

The choice of the actual operative procedure depends, of course, upon the findings, and especially upon the exposure which is possible. An anastomosis is imperative. The anastomosis should be performed as close to the obstructed site as possible, both above and below. This leaves a relatively small blind-pouch area. In both of our cases, it has been possible to anastomose the duodenum with the jejunum. In one it was done antimesocolically; in the second, through the transverse mesocolon. In nineteen of the successful cases in the literature, the type of procedure used was described. In ten of these, a gastroenterostomy was employed, in seven a duodenojejunostomy, in one a gastroduodenostomy, and in one the diaphragm was removed by cautery. If the gall gladder is distended and the infant is jaundiced, a cholecysto-enterostomy must complement the other procedure. This had best be done by uniting the gall bladder with a jejunal loop, rather than a union into the stomach.

The technique of the anastomosis is not too difficult. The distal bowel is completely collapsed. It has been suggested that it be distended with the injection of air or mineral oil. We have not found this necessary, and there may be some difficulty in recognizing the bowel lumen with the exploring needle. A small longitudinal incision into the collapsed bowel will readily disclose the lumen. Then a catheter can be introduced into the lumen, and this delineates the stoma so that suture may be accomplished. We have used two layers of interrupted fine silk sutures for the anastomosis. The finished stoma was about 2 cm. in both cases and appeared to be very adequate.

We have not had any cases in which the biliary tract also needed anastomosis. Judging from our cases of simple congenital biliary tract atresia (Beck, 1949[10]), however, this anastomosis can be performed in the identical manner. The gall bladder can be dissected out of its bed if more mobility is needed. A two-layer anastomosis has been possible in these cases, done in such a manner that the gall bladder is intussuscepted into the lumen of the bowel. This leaves a flap of tissue of the gall bladder in the bowel which will act as a valve and prevent regurgitation.

The postoperative care requires all of the cunning and care that the pediatrician can muster. Any edema at the site of the anastomosis spells trouble, with malfunction of the stoma. This implies great care in the use of fluids. For the first forty-eight hours,

the fluid administered should be low in salt content. Hypoproteinemia and hypopotassemia must not occur. If, as is so often the case, the intravenous catheter fails at the important moment, the infusions may be given intramedullarly. This technique has been eminently safe in our hands, simple and found to be a most rewarding maneuver.[11]

We have permitted oral feedings after twenty-four hours of sterile water. The head is carefully observed for changes in the size and shape of the fontanels. This is an accurate guide. The skin turgor is also helpful, as a mirror of the fluid balance. Electrocardiography is a help in determining the potassium level. We feel that it is probably wise to use antibiotics liberally, as one of our two patients died of an agranulocytosis, in spite of a well-functioning stoma. The protein balance is maintained with the use of blood and plasma. Concentrated plasma is preferable to the amino acids.

It is difficult to estimate the prognosis. We lost one of our two patients, a three pound premature infant, from an agranulocytosis. In Ladd and Gross' report there was one success in five cases. Benson and Penberthy had success in two of three patients. The mortality is unquestionably high. But with proper care, it should be reduced in the future, especially if these patients are located early enough through a suspicious nature on the part of the pediatrician, the obstetrician, and the general practitioner who sees these babies first.

CASE REPORTS

CASE 1.—This baby boy was born after a normal gestation at term. The birth weight was 2.8 kilograms. The physical examination at birth was normal. It was noted that the infant regurgitated all of its feedings from the first. The fluids simply seemed to run out of the infant's mouth soon after feeding. On the following day it was noted that the child actively vomited. A No. 18 French urethral catheter was passed into the stomach and a clear yellow fluid obtained. An x-ray film taken at this time revealed a rather large gastric air bubble, but no gas pattern was seen in the remainder of the abdomen. The chest film was quite normal. The child passed small amounts of normal-appearing meconium.

On the following day the catheter was again passed into the stomach and, under fluoroscopic control, iodized oil was injected into the catheter. A large stomach was revealed and a pouch was observed on the right side of the abdomen which was interpreted as a much dilated duodenum. None of the opaque material was seen to pass what was considered to be the third portion of the duodenum. Farber's test on the meconium was negative.

The child appeared to be quite dehydrated, and he was therefore prepared for surgery by the administration of subcutaneous salt solution. Operation was performed on the fourth day (approximately eighty-eight hours after birth). The anesthetic used was closed ether with an intratracheal tube. The abdomen was opened through a right transrectus incision. The colon was found to be normal in position. The small bowel was completely collapsed. The colon appeared completely collapsed and was very small in caliber. The stomach appeared to be much enlarged and its wall somewhat hypertrophied. The duodenum was very large, appearing to be almost adult size. The duodenum could be followed only to its second portion where it seemed to disappear. The duodenum was opened and no lumen could be found beyond the junction of the second and third portions. There was a definite bile stain to the duodenal fluid so that it was assumed

that the ampulla of Vater was intact. An antimesocolic duodenojejunostomy was performed with two layers of fine silk. A small catheter passed into the jejunum outlined its lumen so that the anastomosis was not difficult. The abdomen was closed without drainage.

For about forty-eight hours the postoperative course was smooth. Then trouble developed. The infant began to vomit. The bowel movements contained bile and blood, revealing that for a time at least the anastomosis was open. Marked dehydration developed with collapse of the fontanels and overlapping of the cranial bones. Chemical studies revealed a severe alkalosis, and hypoproteinemia. Infusions were started by bone marrow with the use of concentrated blood plasma, and Darrow's solution. As soon as the hypocalcemia, the hypoproteinemia, and the dehydration were corrected, the stoma appeared to open and the child was soon able to tolerate rather normal feedings. The infant was discharged on the twenty-fifth postoperative day weighing 3.2 kilograms. His development has been observed for one year and has been normal in every respect. He is eating a normal diet now. At 10 months of age, he weighed 10.3 kilograms.

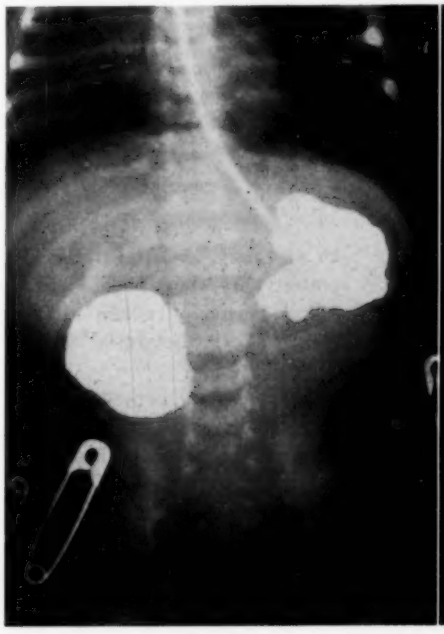

Fig. 3.

Fig. 4.

Fig. 3 (Case 2).—Preoperative film. Note the tremendous size of the duodenal bulb as well as the spasm immediately behind it. Note also the complete absence of gas in the small intestine.

Fig. 4 (Case 2).—Postoperative film. This film was made at the sixth day of life. Note the gas-filled bowel and the absence of any duodenal retention. The stomach, however, is still spastic. This film was taken within a few minutes of the barium swallow.

Case 2.—This infant was born prematurely and weighed 1.9 kilograms at birth. The mother had had a marked polyhydramnion during pregnancy. The infant was placed immediately into an Isolette under oxygen, and

oral feeding was withheld for twelve hours. When feedings were begun, they were regurgitated. At first it was thought that the child was a feeding problem because of its prematurity. He passed a small normal-appearing meconium by rectum. On the third day of life, an x-ray film was taken. This revealed a gastric air bubble, but no gas in the remainder of the film. A No. 12 French urethral catheter passed easily into the stomach and a bile-containing fluid was obtained. Iodized oil injected into the catheter revealed a large stomach. The dye passed through the pylorus into a large pouch but then was regurgitated into the stomach. A diagnosis of duodenal atresia was made.

The infant was hydrated intravenously through a plastic catheter placed intravenously. On the sixth day of life an operation was performed. At this time the infant weighed approximately 1.5 kilograms. The infant was brought to the operating room in his oxygen equipment, and the warmth of the bed was maintained. Anesthesia was induced with rectal Pentothal and nitrous oxide.

The abdomen was opened through a right transrectus incision. The bowel was found to be normally rotated but minuscule in size. The duodenum was tremendously dilated. The third portion of the duodenum was exposed through the transverse mesocolon. A short jejunal loop was brought to this area and a two-layer anastomosis was accomplished. It was not difficult to find and maintain the lumen of the very small jejunum. Again a catheter temporarily placed into the bowel delineated the lining. The abdomen was closed in a layer manner.

The immediate postoperative course was gratifying. The infant took fluids by mouth and vomiting was minimal for about four days. At this time, a film taken of the abdomen revealed gas scattered through the bowel. A small amount of iodized oil administered by mouth passed through the anastomosis and into the bowel. On the fifth day the infant, however, suddenly became much worse. He started to vomit and developed a febrile reaction. Signs of pneumonitis developed. A blood count revealed only 2,100 white blood cells and differential smear revealed only a rare neutrophil. In spite of blood transfusions and other supportive measures, the infant succumbed on the seventh postoperative day. A necropsy revealed a complete atresia of the duodenum between the second and third portions of the duodenum. This structure narrowed down to a fibrous band which was about 8 mm. long. The anastomotic stoma was open. There was a consolidation of the right middle and upper lobes of the lung, and a bronchopneumonia on the left side.

DISCUSSION

In both of these cases the diagnosis might, conceivably, have been established a day earlier. In the second case, the prematurity confused the issue.

In the operative procedure we learned that the most difficult part of the operation is to keep the lumen of the small bowel under vision. The use of a catheter as a probe certainly facilitates this process.

In the postoperative care the adjustment of the chemical balance is all-important. The slightest deviation will permit edema to close the stoma. Chemical imbalances can appear with frightening rapidity. Their recognition, however, is not too difficult, and correction is possible with corresponding celerity. The intramedullary route of infusion is often a boon, when veins are difficult or impossible of cannulization.

The complication of an agranulocytosis, which appeared in the second case, was unexpected and vitiated all of the careful pediatric management in this instance.

SUMMARY

Two cases of duodenal atresia have been presented. In both instances it was possible to perform a functioning duodenojejunostomy. In one of these, a 3-pound 5-ounce premature infant, there was a fatal issue from an agranulocytosis.

The incidence, pathology, perverted physiology, and treatment have been discussed.

CONCLUSIONS

Duodenal atresia is a rare congenital anomaly. It should, however, be diagnosed with greater frequency than appears from the published results.

Surgical management can be successful if the diagnosis is made early enough and especially if a pediatric colleague is available to manage the extremely intricate chemical imbalances which result from the disease, from the anesthesia, and from other sources of fluid and electrolyte loss incident to the operation. In the postoperative care, edema of the stoma can result with complete obstruction from chemical changes alone.

Early diagnosis is possible only if the obstetrician or the general practitioner who sees an infant in the first days of life will investigate any cause of vomiting.

We would like to express our appreciation to Drs. J. M. Higgins, D. M. Motsay, and W. Fisher of the Section of Pediatrics for their help and untiring efforts in maintaining these babies in nutritional balance and for their help in illuminating some of the vagaries of fluid balance in infants.

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FRACTURES OF THE MANDIBLE AND MAXILLA IN CHILDREN

NICHOLAS G. GEORGIADE, D.D.S., M.D.,* FRANK W. MASTERS, M.D.,
JAMES T. METZGER, M.D., AND KENNETH L. PICKRELL, M.D.
DURHAM, N. C.

THE literature is quite replete with reference to the increasing frequency and severity of fractures of the mandible and maxilla in adults[1, 2, 3, 4] and the various methods of reduction and immobilization.[5, 6, 7, 8, 9, 10] However, there is a paucity of information regarding the treatment of fractures of the facial bones in the younger age groups. There is, therefore, a definite need to describe and evaluate the various procedures for the treatment of fractures of the mandible and maxilla in children. Fortunately, cases of fractured jaws in edentulous infants are rare.[11]

IMMEDIATE TREATMENT OF JAW FRACTURES

Whether definite treatment can be instituted immediately depends upon the exclusion of other associated injuries: fractures of the skull, intracranial trauma, subcutaneous injuries of the abdomen and chest, and so forth, which demand precedent. However, even when associated injuries are present, the advice and assistance of the plastic and oral surgeon should be sought immediately to prevent further separation of the fractures or dislocation of the fragments and to maintain an adequate airway. Richards[12] has recently described the type of fractures of the jaw which are most likely to cause *respiratory obstruction*. When transporting young children, it is best to have the face down, without obstructing the mouth, or to turn the head to one side—the side of the fracture, if it is known. In badly comminuted fractures of the mandible, a traction suture or clamp should be placed in the tongue so that it can be pulled forward to prevent obstructing the airway.[13] If forward traction on the tongue does not maintain free respiratory exchange, a nasopharyngeal tube should be inserted. This tube will ensure an adequate airway. It has the added advantage that aspiration of the trachea can be performed easily through it.

The application of bandages and dressings except to cover lacerations or for temporary support is not advisable. The use of "four-tailed" bandages is dangerous and should be condemned.[14, 15] In severe fractures of the mandible, bandages may pull the fragments upward and backward into the oropharynx, thereby obstructing the airway.

Shock may be an indication of blood loss. However, unless there are extensive lacerations to account for the lowered blood pressure and rapid, thready pulse, the astute observer will realize that there are other concealed injuries. Shock, however, should not be identified with nor mistaken for the period of confusion which might accompany a severe blow to the face. No sedatives should be given until a complete survey and an accurate diagnosis have been made and then in

From the Division of Plastic and Oral Surgery, Duke University School of Medicine and Duke Hospital.
*National Cancer Trainee.

only small amounts. Cells and serum should be obtained and the blood cross matched with bank blood. In extreme emergencies 0 negative blood can be used without typing.

DIAGNOSIS OF JAW FRACTURES

Although children are usually apprehensive during the initial examination and while their behavior varies, it is frequently altered adversely by the presence of the anxious parents whose concern is quickly conveyed to the child. Any gross abnormalities in the general contour of the face should be investigated with a minimum of handling. Light palpation will disclose sensitive areas and irregularities of the mandible and maxillae. A careful evaluation should be made of the occlusal relationship, displacement, and mobility of the jaws. The presence of submucosal hemorrhagic areas is usually indicative of a site of fracture.

Radiographs which have been accurately positioned and properly exposed are the most important of the diagnostic procedures. The following positions are most satisfactory. For suspected fractures of the mandible: (A) left and right lateral roentgenograms to show the verticle ramus, angle, and adjacent body of the mandible; (B) posteroanterior position to show the complete mandible; (C) laminagraphs, when available, present accurate visualization of the temporomandibular joints, condyle, and the coronoid processes.[16, 17] Stereoscopic films will suffice when laminagraphs cannot be obtained, although laminagraphs are preferable. For suspected fractures of the maxillae: (A) intraoral films with the occlusal casette placed between the jaws—the angle of the x-ray tube will vary depending upon the area of maxillae to be visualized; (B) the stereo Waters position will

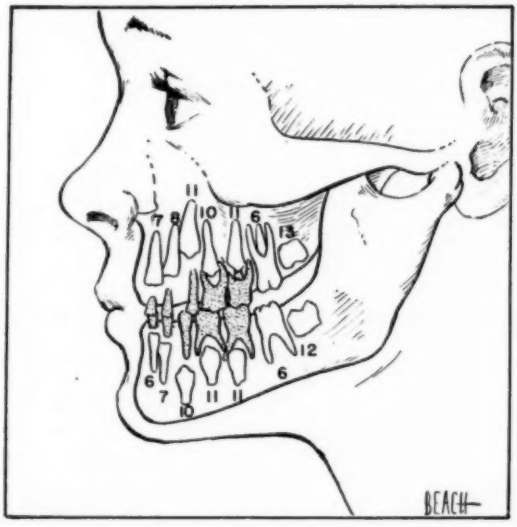

Fig. 1.—Approximate position of deciduous and permanent dentition in a child 6 years of age, with probable eruption time encircled at apices.

usually result in excellent visualization of the maxillae, sinuses, and zygomata.

Fig. 1 shows the approximate position of both the deciduous and permanent teeth of a 6-year-old child.

FRACTURES OF THE MAXILLA

Fractures of the upper jaw in children are most frequently due to a forward fall on the face, such as tripping on a curb, or falling against a protruding object. An object which has been thrown, such as a book, stone, or bat, exerts a similar force. In instances such as this, the head is turned instinctively to one side in an attempt to avoid being struck, and, as a result, the force is usually exerted in an oblique direction.

This type of injury is responsible for many of the fractures of the maxilla in which there is separation or disruption of the labial and buccal plates of bone around the teeth. As a result, the teeth are loosened because of the loss of bony structural support around them.

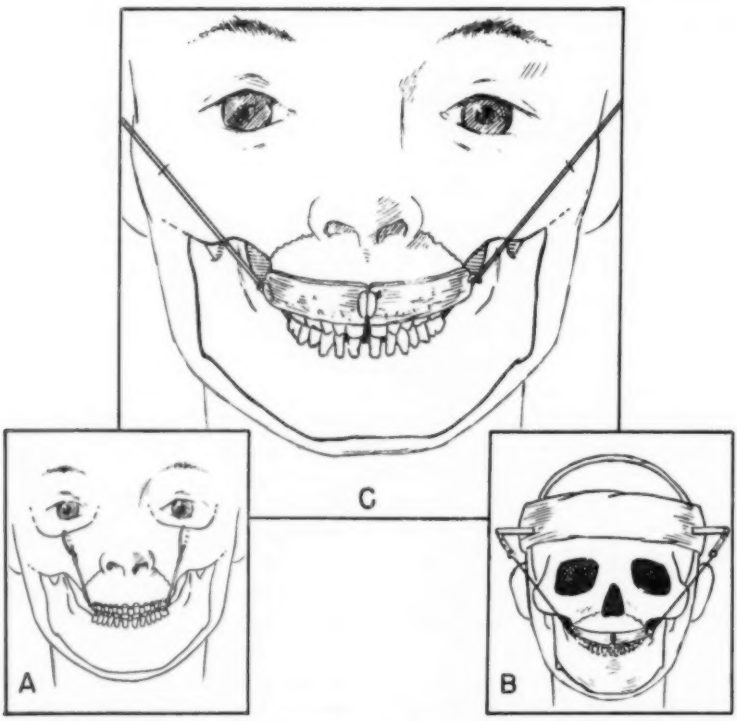

Fig. 2.—*A*, Stabilization of fracture by wires through orbital rim. *B*, Arch bars utilized instead of splint. *C*, Fracture of maxilla or maxillae stabilized by means of acrylic splint connected to plaster head cast by means of stainless steel wires.

Fractures of the alveolar plates are immobilized by supporting the loose teeth on an arch bar which it stabilized on the sound, unaffected teeth. The shape of the crowns of the deciduous teeth and the lack of contacts

may cause some difficulty in proper immobilization. The use of orthodontic bands or caps may then become necessary.[28]

If the fracture is more extensive, an acrylic splint can be made to include the site of fracture as well as the adjacent areas. The splint will stabilize the teeth by fitting snugly around them. When it is possible, the splint is cemented into position. When fixation or stabilization of the appliance cannot be obtained with cement, wire fixation then becomes a procedure of necessity (Fig. 2, *C*).

Fortunately, fractures of the entire maxilla or maxillae are not frequent. These fractures are usually the result of a violent direct blow as would occur upon striking the dashboard of a car, or a blow from a baseball bat. If a sufficient number of sound teeth are present, an arch bar can be wired to the upper teeth (Fig. 2, *A*). It may be difficult to secure anchorage for an arch bar in a child 6 years of age or younger. The application of an acrylic splint over the upper teeth may then become necessary. These splints are made by taking impressions of the upper and lower teeth and related structures. This may necessitate anesthetizing the child for a short period. Acrylic models are then made from these impressions. If distortion from the normal has occurred because of displacement due to the fractures, the models are then cut through at the fracture sites, following which they are reassembled in normal occlusion upon an articulator.[18] A few small hooks should be incorporated in the splint for later use, if necessary. When the splint has been properly seated in the mouth, wires of stainless steel are inserted through the soft tissue overlying the maxillae to connect the splint to a head cast of plaster or cellulose (Fig. 2, *B*).[19, 20] In some instances it may be necessary to extend the cast to the shoulders (Figs. 2, 5, 6).

Some inconvenience and difficulty may be experienced in maintaining a head cast on a child. A procedure which eliminates the use of a cast has been described by Adams[21] who drills a small hole in the infraorbital rim, through which a stainless steel wire is looped around each rim to maintain the maxillae in normal position (Fig. 2, *A*). Displacement in fractures of the maxillae is due to the force of trauma alone, since there are no muscular attachments to cause further separation.

FRACTURES OF THE MANDIBLE

Fractures of the mandible far outnumber those of the maxilla. This is due to several factors: the more vulnerable position of the lower jaw which is composed of cortical bone, its mobility, its horseshoe shape, and the lack of any shock-absorbing mechanism. In contrast, the maxillae are formed of cancellous bone which is soft and spongy, and is supported and protected by the cranium above, by the zygomatic arches in the sides, and by the mandible below.

Uncomplicated fractures of the body of the mandible with little displacement are treated by manipulation of the fragments into proper position and alignment to establish normal occlusion, and then applying a supporting plaster chin cast. (See Fig. 5 for type of plaster-supporting cast.)

Complicated fractures, or those with marked displacement of the fragments, will necessitate reduction under anesthesia and the use of an

acrylic splint. It may be possible to stabilize the splint by cementing or wiring it to adjacent sound teeth. Wiring or banding the teeth of a small child is difficult and tedious for both the patient and the surgeon, even under normal conditions. When a fracture is present, the problems for both the child and operator are accentuated greatly unless the procedure is performed under anesthesia. If the teeth are deciduous, bands or wires cannot be applied wi' out fear of disruption. If the teeth are loose or ab-

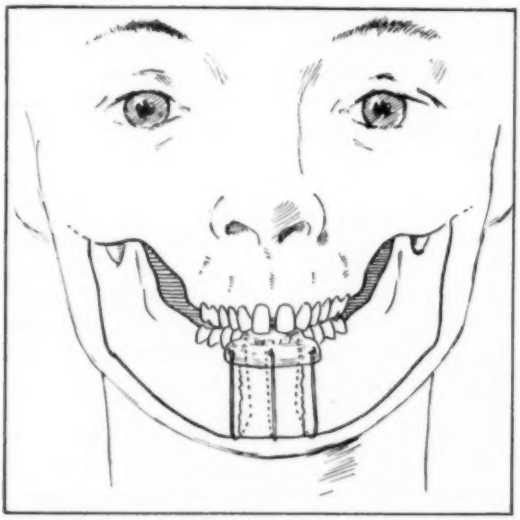

Fig. 3*A*.—Fracture of mandible maintained in correct occlusion by means of circumferential wiring attached to acrylic splint.

Fig. 3*B*.—Lateral x-ray of the mandible showing fracture site in region of the symphysis in a 16-month-old child.

sent, as is frequently the case, circumferential wiring of the mandible and splint then becomes a procedure of necessity (Figs. 3*A*, 3*B*, 3*C*).

The use of extraoral fixation apparatus is necessary only in rare and isolated instances. The routine use of the method is not to be encouraged, since pins driven into the mandible usually cannot be used in the younger age groups because of the deleterious effect on the permanent tooth follicles. To prevent this complication, a number of bone clamps have been described which do not penetrate the cortex of the mandible. Slowes[22] has recently introduced a new extraoral fixation clamp (Fig. 4). However, it is bulky and cumbersome. Depressed or hypertrophied scars may result from skin infection around the pins.

Fractures of the mandible at the angle of the jaw may result in marked displacement of the fragments because of the pull of the masseter muscle. Reduction is accomplished by external traction, which is obtained by placing a wire of stainless steel through a small hole in the posterior fragment and then connecting this wire to a head cast and bar.[23] Elastic traction is applied between the wire and bar (Fig. 5 and insert).

Fractures of the mandible in the region of the symphysis can be reduced and then maintained by the following methods: (a) acrylic splint supported in occlusion by plaster chin cast, (b) circumferential wiring around a splint (Fig. 3), and (c) use of Kirschner wires through fracture site after reduction.[24, 25, 26] The area of the symphysis is usually the only region of the mandible in which a pin can be placed without interfering with the tooth follicles. The pin is then connected to a head cast by means of rubber bands (Fig. 6).

Fig. 3*C*.—A 16-month-old infant immobilized by acrylic splint and circumferential wiring. Normal dietary habits maintained by means of this procedure.

Fractures of the condyle or condyles in young children with minimal displacement should be treated conservatively. Treatment consists mainly in keeping teeth in occlusion, usually best maintained for three or four weeks by means of a light plaster head cast and plaster splint supporting the chin (Fig. 5). An alternate plan is to make a chin strip from heavy muslin and connect it to a light

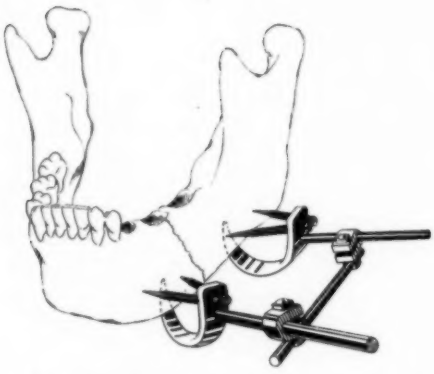

Fig. 4.—Fracture of mandible with edentulous posterior fragment maintained in position with extraoral clamps.

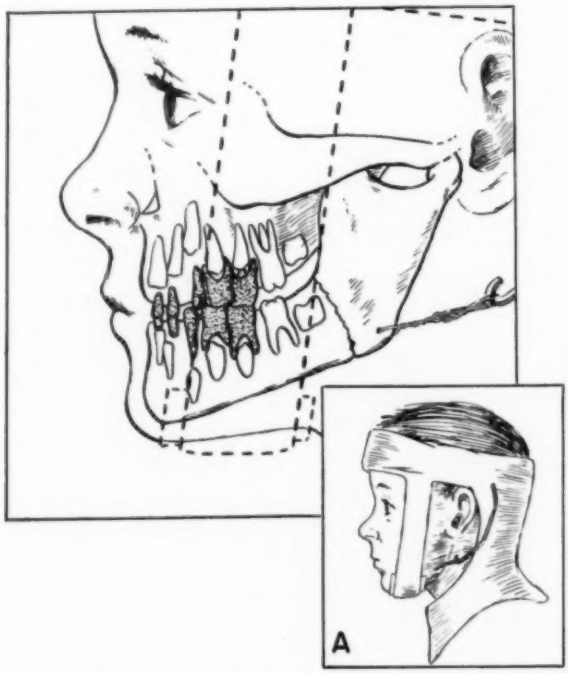

Fig. 5.—Fracture of mandible at angle maintained in position by means of extraoral wire to head cast which is also used to stabilize mandible (*A*).

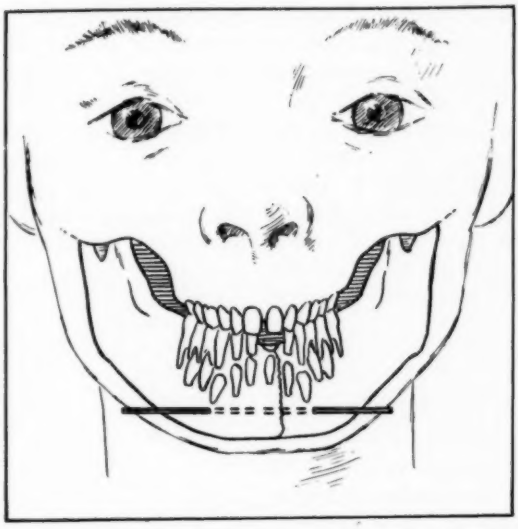

Fig. 6.—Fracture of mandible at symphysis maintained in normal occlusion by means of Kirschner wire.

Fig. 7.—Stabilization maintained with use of heavy muslin chin strap connected to light head cast by means of rubber bands.

head cast by means of rubber bands (Fig. 7).

If there is considerable displacement of the condylar process (usually in a lateral position with overriding of fragments), the patient may have an open bite due to shortening of the ramus. This can be corrected by placing a 2 to 4 mm. thickness of rubber between the upper and lower teeth which then acts as a fulcrum when the teeth are occluded.[28, 29] The shortening on the affected side is partly compensated for in this way.

GENERAL TREATMENT AND CARE OF FRACTURED JAWS

Feeding.—The young children can be fed adequately by administering fluids or semifluids with an Asepto or Chetwood syringe to which a rubber tube is attached. In rare instances it may be necessary to insert a small nasal-gastric tube. Average feeding should consist of one calorie for each centimeter of liquid. Parenteral fluids are calculated on the basis of 100 to 150 c.c. of fluid per kilo of body weight. Daily food requirements for a child are about 90 calories per kilo for a 19-month-old baby to 65 calories per kilo for a 14-year-old.[30]

Mouth Care.—If desired, a mouthwash may be used following feedings. A simple type found most effective consists of 2 grams (½ teaspoon) each of table salt, baking soda, and Borax in 200 c.c. (1 glass) of water. This can be flavored if desired.

Antibiotics.—Penicillin should be administered prophylactically in all fractures of the facial bones.

CONCLUSION

Fractures of the facial bones in children are relatively infrequent. When they do occur, definitive methods of treatment should be instituted promptly. Certain precautions and principles not usually adhered to in the older age groups should be observed. These consist of using an appliance or procedure as simple as possible to restore proper occlusion and function with minimal interference to the deciduous and underlying permanent tooth follicles.

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EFFECT OF EARLY IMMUNIZATION DURING INFANCY ON KIDNEY, LIVER, AND BLOOD TESTS

JOSEPH SCHWARTZMAN, M.D., EDWARD FRIEDMAN, JR., M.D., AND GERALDINE WEIN, M.D.
NEW YORK, N. Y.

INITIATION of immunization[1-10] for diphtheria, pertussis, and tetanus is now encouraged during early infancy, usually at 2 to 3 months of age.

Numerous studies[11-17] have been carried out which demonstrate that kidney function in early postnatal life is not fully developed. Some investigators[18] have found that the level of adult activity may be reached in some infants as early as 10 to 20 weeks, while others[19, 20] noted that none of the kidney function tests in infants under 6 months of age were within adult limits.

It has also been suggested that hepatic function[21-26] in newborn and young infants is decreased as compared with adult activity.

In view of the above and since immunizations have been shown to produce some undesirable and still unexplained effects,[27-30] it was deemed of value to study the effects of these im-

TABLE I. RANGES OF RESULTS OF VARIOUS TESTS

NAME OF TEST	BEFORE IMMUNIZATION	AFTER FIRST SHOT		AFTER SECOND SHOT		AFTER THIRD SHOT	
		FIRST TEST	SECOND TEST	FIRST TEST	SECOND TEST	FIRST TEST	SECOND TEST
Sedimentation rate (Westergren)	5- 22	6- 26	3- 20	2- 18	6- 22	8- 25	3- 22
Complete blood count	All remained within normal limits for age						
Blood urea nitrogen	9- 16	8- 17	7- 12	—	9- 15	10- 14	12- 16
Blood nonprotein nitrogen	26- 34	25- 34	26- 36	—	28- 36	28- 37	25- 33
Blood sugar	55-135	69-129	79-110	65-155	72-130	78-110	68-124
Icteric index	2- 5	1- 4	2- 5	3- 6	—	3- 5	2- 6
Van den Bergh reaction	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Blood cholesterol level	170-220	160-200	170-240	166-220	150-275	—	160-255
Cholesterol esters (%)	65- 80	70- 82	66- 78	79- 80	66- 78	—	75- 82
Total serum proteins	5.2- 8.3	6.3- 7.8	5.2- 7.8	6.7- 8.0	6.3- 7.8	6.0- 8.4	5.8- 7.9
Albumin-globulin ratio	1.8- 2.4	1.7- 2.2	1.6- 2.2	1.7- 2.0	1.6- 2.2	2.0- 2.5	1.8- 2.0

From the Department of Pediatrics, New York Medical College, and Metropolitan Hospital.

munizing agents on other systems of the body. It was decided to observe their effects on the sedimentation rate, blood count, blood urea nitrogen, nonprotein nitrogen, blood sugar, icteric index, van den Bergh reaction, cholesterol and its fractions, total proteins, and the albumin-globulin ratio.

Nine infants, ranging in age from 1 to 4 months and one child 2 years of age, none of whom had ever been immunized, were tested as noted above. Then following each immunization, the tests were rechecked twice at intervals ranging from one to twelve days. The object of this study was to determine whether immunization of young infants would in any way affect the kidney tests, the liver tests, the blood count, or the sedimentation rate of the patients tested. The results of these tests are given in Table I. Results obtained on additional children were discarded since, for various reasons, completion of a full course of immunization was not possible under our supervision.

It was noted that the course of immunization failed to alter appreciably the results of the tests performed.

Since there is a growing tendency toward earlier and earlier immunization, the question of what effects the immunizations may have is an important one. It is of value to know that early immunization does not appear to exert any detectable adverse influence.

SUMMARY

1. Nine infants under 6 months of age and one child 2 years of age were studied with respect to routine immunization.

2. Sedimentation rates, blood counts, kidney and liver tests were not affected to any appreciable extent.

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FAVISM

Report of a Case and Brief Review of the Literature

Vincent dePaul Larkin, M.D.
New York, N. Y.

FAVISM is an acute illness, characterized in its more severe form by hemolytic anemia and hemoglobinuria. Symptoms develop in susceptible individuals who come into contact with Vicia fave, either by inhaling the pollen of the flowering plant or by eating the mature bean. Vicia fave is also known as the fava bean, horse bean, favas, and broad bean.

Favism occurs with great frequency in certain Mediterranean countries, especially Sardinia, with a lesser incidence in Sicily, Italy (Calabria), Greece, Egypt, and Israel. It is said to have been known in ancient times, having been mentioned in the writings of Herodotus, Pythagoras, and Empedocles. Nine[1-8] cases have been reported in the American medical literature, six of them in children.[1, 5, 6, 7, 8] A case in an American child is reported here.

CASE REPORT

D. E., a one-year-old female, of Italian parentage, was seen on July 25, 1952, because of poor color in eyes, ears, and lips for one month. There had been no bruising or blood loss; no recent illness. Her appetite had remained good and her diet normal. No jaundice or discoloration of urine or stools had been noticed. There was no history of familial anemia. Subsequent questioning elicited the history that the child had eaten fava beans for two to three days one month ago, immediately prior to the development of pallor. Physical examination revealed the following: weight 21 pounds 13 ounces, height 29 inches. Nutrition was normal. Moderate pallor of the skin and mucous membranes was noted. No lymphadenopathy was present. Liver was not enlarged, spleen not palpable. Complete blood count revealed: hemoglobin 6.8 Gm., red blood count 3,460,000; white blood count 10,100, polymorphonuclears 30, eosinophils 8, lymphocytes 50, monocytes 12, platelets 230,000, bleeding time 3½ minutes, clotting time 4 minutes; marked anisocytosis and achromia, moderate poikilocytosis and rare stippling; red blood cell fragility test—initial hemolysis .450, complete hemolysis .270; Coombs' test negative. The patient was given Elixir Rubraton t.i.d.

Her color improved rapidly in the following week. Two weeks later the red blood count was 3,860,000 and hemoglobin 8.5 Gm.

DISCUSSION

Favism has a seasonal incidence, cases occurring mostly between April and May when the plant is flowering, and June and July when the mature bean is marketed and eaten. The beans may be dried and eaten at other times of the year but the dried bean loses most of its ability to produce the disease.[6]

Eight of the nine cases reported in the American medical literature have occurred in males; this sex predominance has also been noted in Europe, although females not infrequently have symptoms of favism.

An hereditary factor is well known, with about a 20 per cent familial inci-

Address: 206 Greenway North, Forest Hills 75, N. Y.

dence. Entire families are known to be subject to favism.[3]

Most cases occur in childhood and adolescence, though nursing infants are not immune if the nursing mother or wet nurse happens to include fava beans in her diet.[10] The disease tends to be more severe in children than in adults and almost all deaths due to favism occur in children. The mortality is about 8.0 per cent.[1]

The incidence of favism in the United States is undoubtedly far more common than the reports in the medical literature would indicate. Luisada[9] has pointed out three important reasons why favism should become common in this country. (1) There is a large Mediterranean population in this country. The Italian population in New York City alone is said to exceed that of Rome, Italy. (2) There is extensive cultivation of the fava bean in New York, New Jersey, Illinois, and California. (3) The fava bean is a staple of the diet. It is inexpensive to cultivate in large quantities and very tasty to eat, especially when raw or partially cooked. Furthermore, it has been imported in canned form from Italy. It seems obvious that the mild forms of favism are common, the severe forms less common in this country, being recognized neither by patients nor physicians. A brief discussion of the disease and its common symptoms with a few physicians of Italian parentage sufficed to recall to them numerous individuals among their families and friends who had such symptoms after eating fava beans. Only when the patient is close to death and a clear-cut history of contact with fava beans obtained has the diagnosis been made. Wharton and Duesselman[1] point out that the diagnosis of Lederer's anemia has probably been made in some cases of favism. Robinson[11] noted that many cases of acute hemolytic anemia and hemoglobinuria "blackwater fever" in Tel Aviv, Israel, had been ascribed to malaria, although the peak incidence of these symptoms occurred in March and April when the favas were flowering and the beans eaten, while the peak incidence of malaria occurred in July and August.

Contact with the pollen of the flowering plant of Vicia fave accounts for approximately 40 per cent of cases of favism, the remainder being due to ingestion of the bean. Fermi and Martinetti[12] noted that of their 1,211 cases, inhalation of the pollen caused 459, ingestion of the bean caused 725, and the cause of the remaining 27 was not determined. The plant flowers about one month before the bean matures and its pollen is sticky and of high specific gravity.[9] For this reason it is necessary for a susceptible person to walk through or alongside of a field of fava plants to develop the disease by inhaling the pollen. The amount of fava bean ingested bears little relation to the severity of the disease. Luisada[9] has seen favism develop in a 5-year-old child after eating a single bean, other cases from drinking water from a container in which leaves from the fava plant were kept for some time or from drinking milk obtained from a goat, only when the favas were added to the goat's diet, since they are not a normal constituent of the diet of the goat.

Symptoms develop in a few seconds to hours when the pollen is inhaled, in five to twenty-four hours when the bean is eaten. Hutton's patient[3] had attacks of favism as a child in Sicily, in which he would become unconscious immediately after walking past a field

of flowering fava plants. He developed favism as an adult twenty-four hours after eating fava beans.

In the severe form of favism due to inhalation of pollen there is a rapid onset of dizziness followed by collapse and unconsciousness; several hours later there is pallor and bloody urine. Milder cases complain of malaise and dizziness with gradual onset of nausea, repeated yawning, vomiting, chills, pallor, lumbar pain, and fever. Later jaundice and hemoglobinuria develop.

Symptoms of favism due to ingestion of the bean are similar to those described for inhalation of the pollen but the rapid onset of unconsciousness does not occur. Clinical symptoms vary in severity, according to Gasbarrini.[13] There may be an abortive form with headache, nausea, pain in the extremities, and pallor. Even milder cases, seen by Luisada, complain only of headache and slight fever for a few hours, often being diagnosed as migraine. Other degrees of severity include: a mild form with addition of moderate anemia, icterus, and slight hemoglobinuria; a grave form with weakness, prostration, marked pallor, moderate icterus, scant and bloody urine, diarrhea and vomiting; a fulminant form seen mostly in children, with intense anemia, hemoglobinuria, and shock in addition to previously mentioned symptoms; a hemorrhagic form with petechiae and ecchymoses, terminating fatally. Special forms have been described—an icteric form, in which icterus is the only symptom, and an urticarial form, in which there is urticaria of the hands and face with intense itching. Blindness has also been described.[13]

Physical examination reveals varying degrees of pallor and icterus of the skin and mucous membranes, rarely petechiae and ecchymoses, apathy, weakness, and shock. Sclerae are icteric. There is a tachycardia and frequently a systolic murmur may be heard over the precordium. The liver may or may not be palpable. The spleen is often palpable and slightly tender.

Laboratory findings are as follows:

There is a normocytic anemia of considerable severity with hemoglobin often as low as 4.0 Gm. Aniso- and poikilocytosis are present. Reticulocytes are increased and may reach 30 per cent. Oval, target, and spherical cells are usually not seen though they may be present.

Erythrocyte f r a g i l i t y is normal. Leukopenia, neutropenia, and thrombocytopenia are said to occur in the first few hours to be followed by a reversal to leukocytosis, polynucleosis, and thrombocytosis. Eosinophilia may occur. The icterus index is moderately elevated for a few days and there is a positive indirect van den Bergh test. The Donath-Landsteiner test for paroxysmal cold hemoglobinuria is negative. Blood urea nitrogen may be increased, uric acid decreased. Blood sodium may fall to one-half normal and potassium may increase up to three times normal concentration. The latter is due to release of potassium from hemolyzed erythrocytes, the potassium loss being closely related to the escape of hemoglobin.[14] Urine is usually deep red or bloody in color. Reaction may be acid or alkaline. Three to 4 plus albumin, granular casts, and hemoglobin are present. A few red blood cells may be present. The urine returns to normal in three to four days.

Skin tests and passive transfer tests may be negative for some weeks after

an attack.[3] Mild symptoms of favism may be precipitated by intradermal injection of a test dose of fava bean antigen.[2, 4] Positive skin tests and positive passive transfer tests by the Prausnitz-Küstner technique have been demonstrated in some patients.[16]

The mechanism by which hemolysis of erythrocytes is brought about is not known. It is generally accepted that the disease is due to a hypersensitivity to one or more allergens in the pollen, plant, and mature bean of Vicia fave.[9] The production of hemolytic anemia and hemoglobinuria in rabbits by injection of fava bean antigen may not be significant since the same condition may be produced in rabbits with ordinary lima beans. The Arneth-Landsteiner test for paroxysmal hemoglobinuria has been negative.

Treatment is symptomatic. If there is shock, epinephrine is of value. Transfusion of whole compatible blood is necessary if a significant degree of anemia occurs. Prevention of favism in susceptible persons requires avoidance of fields in which the plant is flowering, and not eating fava beans.

SUMMARY

The seventh case of favism in a child in the United States is reported. The clinical picture of favism is summarized.

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FUNCTIONAL DISORDERS OF THE LARYNX IN EARLY INFANCY

ABRAHAM B. SCHWARTZ, M.D.
MILWAUKEE, WIS.

"The newborn baby does not by any means start from scratch. He is at birth already in possession of all the nerve endings he will ever have. These cells have much capacity for learning; but to no small extent their organization has been either fixed or channelled by the countless generations of a past which stretches back into a vista of a billion years."

—*Arnold Gesell and Frances L. Ilg.**

THE newborn infant is equipped with many delicately balanced physiologic reflex mechanisms which enable him to cope with the challenges of his new external environment. The reflex of opening and closing the larynx is one of these. Reflexes in early infancy often lack the integrated pattern they achieve in the mature child. Functional disturbances of the larynx which are explainable by immaturity or the imbalance of the laryngeal opening and closing reflexes are frequently seen by the pediatrician. Because of their transitory character, they have received scant attention in medical literature.

Illustrative cases of four such disorders are here presented along with an interpretation of their etiology.

1. Deglutition apnea.
2. Congenital laryngeal stridor.
3. Stridor with dysphagia.
4. Exudative laryngeal stridor.

The safety of the pulmonary airway imposes the necesssity for the immediate closure of the glottis with every swallowing act, as well as with other threatening experiences. This function is performed in the most primitive type of larynx by a sphincteric muscle.[1] Since the swallowing of the amniotic fluid is a normal and continuing physiologic function in fetal life,[2, 3] the glottic closing reflex must find frequent rehearsal in the aquatic environment of the fetus. The demands for opening of the glottis, on the other hand, do not become imperative until after birth, when the competing needs of breathing and swallowing call for split-second balance between these two acts.

From the Department of Pediatrics, Marquette University School of Medicine, and the Milwaukee Children's Hospital.

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DEGLUTITION APNEA

To the casual observer, the hungry infant takes his feeding without pausing to breathe. Roentgenkymographic studies in the infant have shown, however, that food flows over the laryngeal compartment during an apneic interval lasting 0.15 to 0.18 second. This interval may occur between inspiration and expiration or between expiration and inspiration.[4]

When, in the immature infant, the larynx is closed for a longer time than usual, apnea and cyanosis may occur. An illustration from Hofmann and Peiper (Fig. 1) illustrates the prolonged apenic pause in an immature infant. The following case history is an example of deglutition apnea seen in my practice.

Illustrative Case.—R. C., a male infant, was born Aug. 8, 1951, at St. Mary's Hospital following a seven months' pregnancy. The delivery was spontaneous. The birth weight was 3

pounds. The examination note at the initial examination states, "Condition satisfactory. Color good. Cry fairly good. Responds to stimuli. No abnormalities." When 19 days old, the infant had a brief gastrointestinal upset with fever which responded to penicillin and subcutaneous fluids. At the age of 1 month, cyanotic spells were reported. These occurred for the most part at feeding time. Physical examination disclosed nothing unusual. Roentgenogram of the chest showed "lungs clear, heart, normal size, position, and contour. No evidence of enlarged thymus." A diagnosis of deglutition apnea was made. The nursery personnel were instructed to allow time for the infant's breathing by removing the bottle every few seconds. When this was done, no further episodes of cyanosis occurred during the hospital stay nor after the discharge home.

been the subject of a peculiar form of obstructed inspiration,"[5] it has been generally held that congenital laryngeal stridor is caused by an anatomically abnormally shaped larynx. Wilson[6] has recently re-emphasized two reasons for doubting this theory. To these a third may be added. These reasons are: (1) the same type of larynx may be seen in patients who have no stridor; (2) stridor may occur in a child with a normal "omega-shaped" glottis; (3) stridor may disappear without any apparent change in the laryngeal configuration.

The stimuli to which the swallowing reflex responds during fetal life must often create opportunities for stereotyped conditioning of the laryngeal

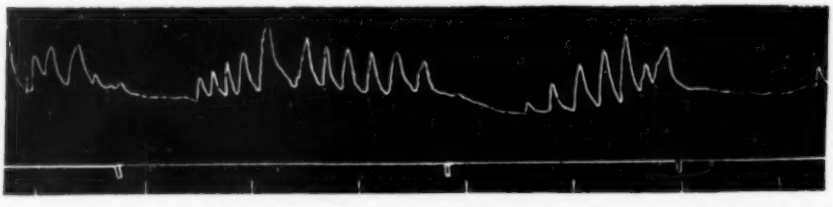

Fig. 1.—Upper curve respiration. Lower curve deglutition. After every swallowing act, apneic period is shown. (From Hofmann and Peiper: Klin. Wchnschr. 14: 1723, 1935.)

CONGENITAL LARYNGEAL STRIDOR

The subclinical forms of a disease frequently outnumber those with prolonged signs and symptoms. The laryngologist's experience with congenital laryngeal stridor is obviously restricted to those instances with considerable difficulty in breathing. Because of this, both the frequency and character of the more numerous minor instances of stridor seen by the pediatrician have been disregarded.

Since David Lee's first presentation to the London Pathological Society of the "larynx from an infant which has

closing mechanism in the postnatal period. As a result of such conditioning, an incurving laryngeal configuration might result. The repetitive performance of laryngeal closure would constitute a clinical counterpart of the cadaver experiments of Thomson and Turner,[7] experiments in which they were able to duplicate the incurving laryngeal structures by repeated forcing of air through a metallic tube inserted into the trachea.

The hypothesis is therefore proposed that congenital laryngeal stridor is the result of repetitive laryngeal closing

experiences, a neuromuscular conditioning provoked by the swallowing act, which has its inception in fetal life.

This hypothesis would explain why stridor frequently occurs in infants with excessive food regurgitation habits, in which cases neuromuscular reflexes often lack mature integration. It would explain why with the maturity of the physiologic reflex, stridor disappears, though the anatomic configuration may remain unchanged.

Illustrative Case.—B. W. was a healthy infant at birth. It was noted that there was an excessive oral mucus. He was breast fed on a demand schedule. At 6 weeks of age, despite a full diet of breast milk, cereal, fruits, and vegetables, he cried excessively, and did a great deal of regurgitating. This was somewhat improved following the use of antispasmodic drugs. Stridor was pronounced, and could be heard at some distance. At about 5 months of age, the stridor practically disappeared, and regurgitation of feedings was markedly improved.

CONGENITAL STRIDOR WITH DYSPHAGIA

It is commonly stated that in congenital laryngeal stridor there are no symptoms other than those due to laryngeal malformation. This statement does not agree with pediatric experience. The observation is obviously due to the fact that in pronounced examples of the disease, the laryngeal symptoms overshadow all others. The association of congenital laryngeal stridor with symptoms of pylorospasm has received scant attention, although occasional case histories casually mention feeding difficulties. A minor degree of stridor may be heard in most infants with pylorospasm. This stridor may vary from mild squeaks or barnyard cackling noises heard during avid feeding moments to the air fighting stridorous struggles which make each feeding incident an ominous experience. M'Kenzie,[8] reporting an unusual case of laryngeal stridor with dysphagia in a 3-year-old child, quotes Ashby as saying that "in exceptional cases, a difficulty or spluttering in swallowing is associated with congenital laryngeal stridor." This is the only note I have been able to find in the older literature of these associated symptoms.

Illustrative Case.—M. W. was born in February, 1952. His birth weight was 6 pounds 11 ounces. At 3 weeks of age he was a "gassy," crying baby. At 7 weeks of age, he did a good deal of food regurgitating, and had excessive nasal snorting. He made satisfactory weight gains. Bentyl hydrochloride was prescribed for the control of regurgitation. The infant was still stridorous. The mother reported that when he took his bottle feeding, swallowing movements were frequently interrupted by choking, coughing, and spluttering. I confirmed this observation by watching a feeding given at my office. Struggling during feeding, as well as stridor, became less as the child grew older. It did not take place with every feeding. Roentgenographic examination gave no evidence of enlarged thymus or of vascular rings. Laryngoscopy recorded the usual relaxed infantile larynx.

EXUDATIVE STRIDOR

Whatever the cause of the stridor, increased mucus secretion from the well-supplied mucous glands of the larynx may aggravate the already embarrassed airways. Excess mucus may incite sudden episodes of vomiting, choking, pallor, and collapse. Many cases recorded in the older literature as thymic stridor seem to belong in this category.[9] In the discussion of a paper on thymic stridor by Wasson before

the children's section of the American Medical Association in 1927, Dr. James Walton suggested that certain symptoms of the group of cases called thymic stridor could be attributed to excessive mucus secretion. These, he said, could be relieved by atropine, an effect I have also observed in exudative types of congenital laryngeal stridor. These exudative types in particular suggest an allergic component in the pathogenesis of congenital laryngeal stridor.*

It is interesting to recall that Barthez and Rilliet,[11] who have been credited with the first clinical description of congenital laryngeal stridor, give a vivid description of the exudative manifestations. "The most characteristic symptom was the humid stertor, a real tracheal and very abundant gurgle, especially pronounced after coughing, and when some one excited the child. . . . It seemed as though a fit of coughing was enough to bring it on and then another to make it disappear. . . . It seemed as if the expectoration could be so easy that we did not understand why the sputum did not loosen immediately and pass into the stomach, but no such thing occurred; the stertor persisted, and if it disappeared for a moment, it was because the child had calmed down, for as soon as the child became excited, the noise started again."

It is often stated that congenital laryngeal stridor is in itself rarely a cause of death. In his recent discussion of the subject, Wilson suggests that some of the great number of infants whose deaths are reported as due to suffocation or overlaying really die from congenital laryngeal stridor. An illustrative case which occurred in my practice is here recounted.

Illustrative Case.—S. M., a 2½-month-old infant, was brought to the office with the complaint of excessive regurgitation and excessive mucus. The infant had congenital laryngeal stridor. At 3 weeks of age he had a spell during which his nurse reported he became limp and pale. The infant was hospitalized for roentgenographic and laryngoscopic study. Both proved uninformative. There was no evidence of pulmonary, cardiac, or thymic abnormality, though stridor and regurgitation continued. The nutritional state was satisfactory. At the age of 5 months, after having been put down following his evening feeding, the infant was found dead. Necrospy was not performed.

Departing for a moment from the compulsion of seeking an explanation on the organic plane, the possibility suggests itself that death in congenital laryngeal stridor may result from an overzealous reflex of laryngeal closure during the threatening experience of regurgitation. In the struggle engendered by regurgitation, it would seem that the threat to the pulmonary airway would be greater in infants with congenital laryngeal stridor.

SUMMARY

Attention is called to four types of functional disorders of the larynx in early infancy. They are (1) deglutition apnea, (2) congenital laryngeal stridor, (3) stridor with dysphagia, and (4) exudative stridor. A new interpretation is offered to explain the cause of congenital laryngeal stridor.

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A CASE OF CONGENITAL SYMPATHOGONIOMA (NEUROBLASTOMA) OF THE RIGHT ADRENAL SIMULATING ERYTHROBLASTOSIS FETALIS

LEROY W. FALKINBURG, M.D., AND MAURICE N. KAY, M.D.
PROVIDENCE, R. I.

IT IS well known that neuroblastoma of the adrenal medulla, while quite uncommon, is not extremely rare. On the other hand, congenital neuroblastoma is a very rare lesion. Wells[1] in a paper reviewing the subject of congenital malignant tumors, published in 1940, could find only seventeen cases of congenital neuroblastoma definitely present at birth, fifteen cases probably congenital, and twenty-one possibly congenital cases.

Kouyoumdjian and McDonnald,[2] in a recent article, have collected nine additional cases of congenital neuroblastoma published between the years 1940 and 1951, and added a case of their own diagnosed as congenital neuroblastoma with multiple congenital anomalies.

A further search of the literature has brought to light several additional cases. Larimer[3] reported a case of adrenal sympathogonioma in a newborn Negro female who died nine hours after birth. Beck and Howard[4] described the case of a white male infant in whom an abdominal mass was discovered three weeks after birth. A biopsy revealed the presence of a neuroblastoma and intensive radiotherapy was instituted. Seven years later the child was alive and apparently well. Cervini, Moran, and Sanchez Basso[5] cited a case of embryonal sympathoma of the right adrenal with hepatic metastases. The patient was a female infant in whom abdominal enlargement was observed ten days post partum. Finally Brody[6] reported a case of congenital neuroblastoma in one of twin girls.

From the Departments of Pediatrics and Pathology, Roger Williams General Hospital.

We shall not attempt to give a detailed account of the history and embryologic interrelationships of this type of tumor in view of the fact that such information is available in many other publications. We shall limit ourselves to stating that Scott, Oliver, and Oliver[7] have subdivided these tumors into four categories according to the degree of anaplasia or differentiation. Passing from the most anaplastic to the most differentiated forms, they recognize: sympathogonioma, sympathoblastoma, neuroblastoma, and neuroeytoma.

With these several considerations in mind, we wish to report the following case.

CASE REPORT

Mrs. C. M., aged 32 years, para ii, was admitted to the Roger Williams General Hospital, Providence, R. I., at full term on April 22, 1949. A cesarean section was immediately done owing to premature rupture of the membranes, continued strong uterine contractions without satisfactory cervical dilatation, large fetal size, and increasing rate of the fetal heart. One other child was born in 1947 and was living and well. The mother's history and physical examination were not remarkable and the present pregnancy had been normal until the onset of labor. There was no history of miscarriages, stillbirths, or premature labor.

Laboratory studies on the mother yielded the following information. The urine showed 4 plus acetone but was otherwise negative. The hemoglobin was 10 Gm. per 100 c.c. and her red count was 3,200,000. The Wassermann and Hinton tests were negative. Her blood was found to be

Rh positive, type O. Later a sample of her blood was sent to Dr. Fred Allen at the Blood Grouping Laboratories of the Children's Medical Center, Boston, Mass. This sample was titrated for anti-A agglutinins and showed a clinically insignificant titer.

The patient was delivered of a female infant weighing 7 pounds 9 ounces, with an estimated maturity of about 8½ months. The mother made an uneventful recovery. Pathologic examination of the placenta was negative.

Immediately after birth the infant exhibited marked abdominal enlargement associated with marked and progressive jaundice. The abdominal enlargement was clinically regarded as resulting from pronounced splenomegaly and hepatomegaly. Radiographic studies indicated a marked enlargement of the liver and spleen with downward displacement of the stomach and intestines. These findings, associated with the pronounced icterus and normoblastemia, immediately raised the question of erythroblastosis fetalis.

Laboratory work done on the child yielded the following information. Hemoglobin was 15.5 Gm. per 100 c.c. The red count was 3,670,000 and the white count was 19,300. The differential count showed metamyelocytes 3, stabs 16, neutrophilic segmenters 36, lymphocytes 32, large mononuclears 12 and eosinophils 1. For every 100 white blood cells there were normoblasts 35, pronormoblasts 2, and erythroblasts 1. The red cells displayed anisocytosis, poikilocytosis, and polychromasia. The child's blood was, in addition, Rh negative, type A.

Despite vigorous therapy, consisting of blood transfusions and various supportive measures, the condition of the child became progressively worse and she died five days after delivery.

Autopsy Findings.—The body was that of a markedly jaundiced, well-developed female infant measuring 18 inches in length and weighing about 10 pounds. External abnormalities consisted of marked icterus, pronounced abdominal distention, and anasarca. There was remarkable edema of the labia. All tissues were found to be very edematous upon incision.

The liver, in situ, was much enlarged, weighing 650 grams and almost completely filling the entire abdominal cavity, with downward displacement of the stomach and intestines. Externally the liver was mottled, presenting yellowish orange splotches against a dark purple background. The liver sectioned easily and the sectioned surface was mottled and variegated, presenting large and small brownish purple to yellowish brown areas in every conceivable combination.

The spleen weighed 10 grams and was not abnormal.

The left adrenal weighed 7 grams and was grossly normal. The right adrenal was not identified as such. It was replaced by a large tumor mass weighing 52 grams, and measuring 5 × 5 × 3 cm., which displaced the right kidney downward. The mass was very soft to the touch and showed a mottled yellowish brown color, and was invested by a thin capsule. Section revealed a soft, moist, rather homogeneous cut surface, in the center of which there was a ragged brownish degenerated area.

The remaining viscera exhibited no obvious gross abnormalities.

Microscopic Examination.—The right adrenal medulla was completely replaced by large and small masses of anaplastic tumor cells separated by areas of hemorrhage and necrosis. In many areas the growth was seen to encroach upon the cortex. The cells were somewhat larger than small lymphocytes, with nuclei in which small clumps of chromatin were diffusely scattered. A thin rim of cytoplasm was barely visible or no cytoplasm was seen at all. Mitoses were found but only after considerable search. Rosette formation was not observed and it was impossible to demonstrate neurofibrils.

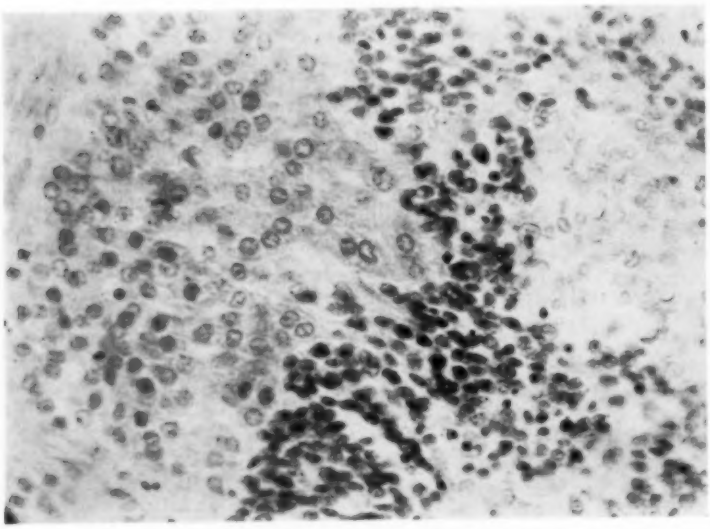

Fig. 1.—Sympathogonioma of adrenal medulla.

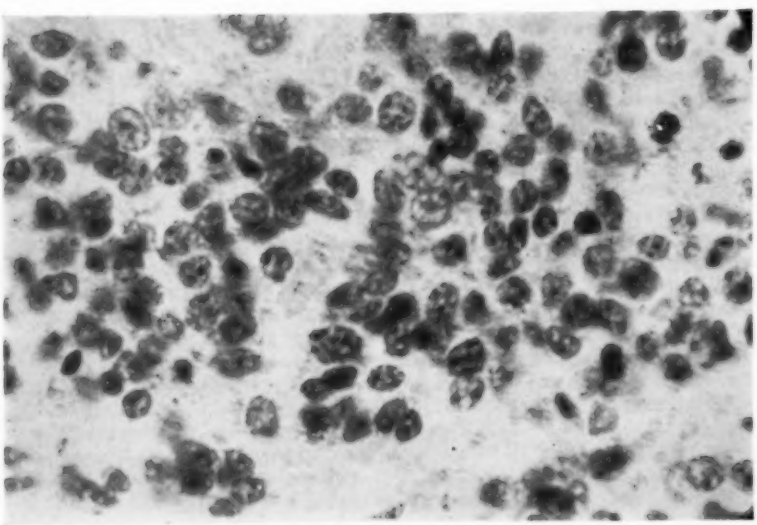

Fig. 2.—Sympathogonioma of adrenal medulla metastatic to liver.

The liver substance in most areas was almost completely replaced by tumor cells corresponding to the above description. Those hepatic cells still remaining were the site of severe fatty change.

Study of the remaining viscera microscopically revealed microscopic metastases in the visceral pleurae, cerebellar leptomeninges, and in the left periadrenal fibrous tissue.

Frozen sections from the basal ganglia failed to show evidence of kernicterus.

Pathological Diagnosis.—Sympathogonioma of the right adrenal medulla, with massive metastases to the liver and microscopic metastases to the visceral pleurae, cerebellar leptomeninges, and left periadrenal fibrous tissue.

DISCUSSION

We regard this tumor as a sympathogonioma, inasmuch as we were unable to demonstrate rosettes or neurofibrils. We consider the case worth reporting from two standpoints. The first and most important feature is that it is unquestionably a congenital form of this type of tumor and congenital tumors of this type are sufficiently rare to warrant attention.

The second feature of interest is the fact that the clinical and laboratory data, to a certain point, gave rise to the suspicion that the case was one of erythroblastosis fetalis. This presumption was based on the rapid development of profound icterus, clinical evidence of marked hepatic and splenic enlargement both by palpation and radiographically, anemia, leukocytosis, and normoblastemia. The mother was, however, Rh positive and the child Rh negative, so that the ordinary form of erythroblastosis was excluded. Then the possibility of maternal sensitization to the fetal A factor was considered, but the maternal serum failed to show a significant titer of anti-A antibodies. For these reasons the possibility of erythroblastosis was excluded on clinical and laboratory evidence before the case came to autopsy.

SUMMARY

A case of congenital sympathogonioma (neuroblastoma) of the right adrenal medulla, with massive hepatic metastases, and microscopic metastases to the visceral pleurae, cerebellar leptomeninges, and left periadrenal connective tissue, is reported.

The rarity of this type of neoplasm is stressed, as well as the fact that clinically it simulated erythroblastosis fetalis during its earlier clinical course.

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PULMONARY LEIOMYOSARCOMA IN A CHILD

W. PRICE KILLINGSWORTH, M.D.,* PORT ARTHUR, TEXAS, AND
GEORGE S. MCREYNOLDS, M.D., AND A. WILSON HARRISON, M.D.,
GALVESTON, TEXAS

PULMONARY leiomyosarcoma is one of the rarest of chest tumors in children. A review of the literature[1-14] and communication with the tumor registry[15] of the American Academy of Pediatrics fails to reveal a previously recorded case in a child. Nine of these mesenchymal tumors of the chest have been reported in adults, five of which were benign.[13]

CASE REPORT

D. T. was a 7-year-old girl whose birth weight was 6 pounds (2,750 grams). She had been bottle fed. The feeding and developmental history was normal except that the child was always lean and lank as are her parents and other siblings. She had had repeated colds and sore throats, had been immunized against pertussis, diphtheria, tetanus, and smallpox before entering school. She had had chicken pox, rubella, and rubeola. The mother and father, two older sisters, and one younger brother were living and well. Maternal grandfather, aged 66, died of pulmonary tuberculosis, November, 1948. All children were exposed to him over a period of two weeks. In April, 1949, the child developed "bronchitis" following an attack of the "flu." This was characterized by cough, low-grade fever, anorexia, and a weight loss of three pounds. After two weeks she seemed well. The last week in June, 1949, she developed a fever of 105° F., with follicular tonsillitis, swollen anterior cervical lymph nodes, and vomiting. After four days she was well, having been treated with penicillin and sulfadiazine. Her chest was clear. During the first week of July she began to complain of "smothering spells" (no cyanosis) when she ran and played. Her appetite was poorer than usual and her mother thought she had had some fever but it was never recorded. At this time the family physician checked her and found nothing except a mild secondary anemia for which he prescribed a tonic.

The child did well during the summer months but with the beginning of school in September she again began to complain of "smothering spells," had a poor appetite, no vigor, was listless in school and did not wish to play with the other children. She complained of pain in her left chest on one or two occasions after exercise. This was mild and transient in nature. She had no illnesses but had lost four pounds of weight, 34¼ pounds (15.6 kilograms) to 30½ pounds (13.8 kilograms) in four months. Her height was 42¾ inches (110.4 cm.). At this time the maternal grandmother was hospitalized for pulmonary tuberculosis. The parents became alarmed and brought the child in to one of us for complete examination (W. P. K.). At this time, Sept. 19, 1949, the child was pale, listless, but afebrile. The hemoglobin was 63 per cent, color index 0.85, red blood count 3,770,000, white blood count 8,800, polymorphonuclears 62 per cent, lymphocytes 38 per cent. Red blood cells showed moderate achromia. No abnormal white cells. Urine negative. Stool examination was negative for blood and parasites. Physical examination was entirely negative except for hypertrophic tonsils, moderately enlarged anterior cervical glands, and diminished breath sounds over left chest posteriorly. Respiratory move-

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*Address: 541 Ninth Ave.

ments, left chest less than on right. An occasional sticky râle was present. Percussion notes moderately dull. There was no cough. The left thoracic cage seemed smaller than the right. Because of the tuberculosis contact rather than the physical findings, the child was sent for fluoroscopic and x-ray examination of chest. Tuberculin (O.T.) was 1:10,000 and 1:1,000 negative. Coccidioidin test was negative on Sept. 23, 1949.

Dr. M. A. Cunningham, county tuberculosis physician, gave the following fluoroscopic report: "Entire left side of the chest has a fairly dense homogeneous shadow. A small portion of the right border of the heart is visible. The stomach bubble is in normal position. The left leaf of the diaphragm is not visualized. The right side of the chest is clear. Would consider left-sided atelectasis on nontuberculous basis. If the shadow (left-sided) is due to fluid, the heart should be pushed to the right." On the same day, Dr. F. Y. Kuhlman gave the following x-ray report: "The left chest is uniformly, diffusely opaque with no air-containing lung visible, except for some of the right lung which extends over past the spine, to the left, in the upper lung field. No delineation of the heart shadow on the left, nor of the left diaphragm. Left interspaces are narrow and the chest is asymmetric. No vertebral deformities (hemivertebrae) such as are frequently seen in aplasia of the lung. The trachea is displaced to the left, and we are unable to identify the outline of a left main bronchus. Right lung shows hyperventilation, but no evidence of disease.

"This could be a congenital agenesis or aplasia of the left lung, or an atelectasis. If the latter, it is absolutely complete—no vestige of an air-containing left lung is present. Foreign (nonopaque) body and neoplasm should be ruled out."

On Sept. 30, 1949, the child was bronchoscoped at St. Mary's Hospital by Dr. B. H. Vaughan, under general anesthesia, and he gave the following report: "The larynx and trachea are normal as is the right main bronchus. Approximately ¾ inch down the left main bronchus is a smooth reddish mass that fills the lumen and the scope will not pass. Biopsy taken and Lipiodol introduced. Impression: bronchial tumor." The x-ray report following bronchoscopic manipulation was as follows: "The films made immediately after bronchoscopy show some air in the left lung, both the upper and lower lobes, with no definite soft tissue masses visible in the lung. The Lipiodol outlines the beginning of the left main bronchus for a distance of about ¾ inch only. Right lung shows considerable prominence of the trunk shadows, probably hyperemia.

"A later film made on the Bucky shows still more air in the left lung. The heart and mediastinum are still shifted to the left, but for the first time the left border of the heart is plainly visible, and the diaphragm can also be seen. Traces of the Lipiodol are in the left lung, but not sufficient to enable one to draw any definite conclusions. No definite lung tissue lesion seen in so far as the lung is aerated at this study."

The tissue report by Dr. H. B. Williford revealed the following: "Tissue from left main bronchus. Description: Two small, glistening, gray tissues 1 mm. and 2 mm., firm to touch. Microsection: Shows a tissue of organized hyaline material which is acellular, and one small fragment of benign bronchial epithelium."

The child's condition remained unchanged except for periodic smothering spells (no cyanosis) and on Jan. 30, 1950, she was admitted to John Sealy Hospital, Galveston, Texas, for further study. There still was no history of productive cough or hemoptysis.

Physical examination at the time of admission was essentially negative except for the respiratory system. This was recorded as showing de-

creased respiratory movements on the left. Fremitus was slightly diminished over the left lung field. Breath sounds were definitely diminished on the left side.

On several occasions, the patient was bronchoscoped (by G. S. M.) and at each examination, a smooth, reddish tumor was visualized in the left main bronchus at the level of the upper lobe bronchial orifice. Repeated biopsies were done and on each occasion, the report was nonspecific granulomatous inflammation. There were four biopsy reports recorded in the patient's chart between Jan. 30 and Feb. 16, 1950.

The patient was discharged from the hospital. However, she was readmitted on March 28, 1950. Several roentgenographic studies had shown a persistent atelectasis of the left lung and in view of the endoscopic appearance of the tumor, it was felt that an exploratory thoracotomy should be done. Consequently, on March 30, 1950, this operation was performed (by A. W. H.).

With the patient in a tilted supine position, the left chest was opened through a submammary incision and spreading the third and fourth ribs. There was considerable fluid in the pleural space, but whereas the upper lobe was aerated, the lower lobe was found to be distended by a rounded firm mass. There were fairly dense adhesions to the diaphragm and over the lateral aspect of the lower lobe. Since there appeared to be no extension into the hilum of the lung and no metastasis into the mediastinal nodes, dissection of the hilum was begun. The pulmonary artery and superior pulmonary vein were individually ligated and divided. When dissection was turned upon the inferior pulmonary vein, however, it was

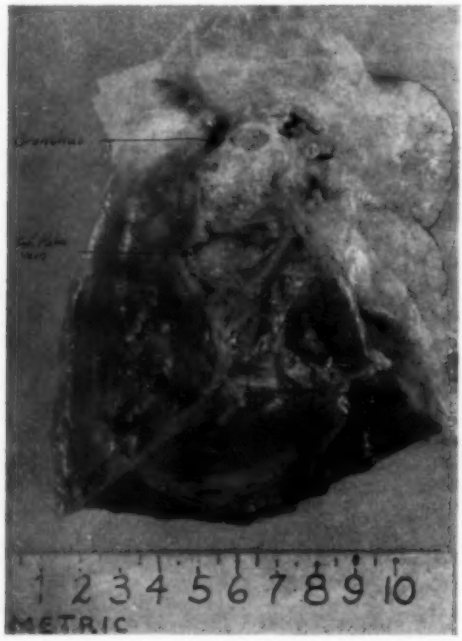

Fig. 1.

found to be almost twice the normal size and to be quite firm as if it contained a tumor or an old thrombus. Since the tumor mass considerably hampered further dissection in the region of the left atrium, the vein was ligated and divided. Immediate pathological examination revealed a neoplasm which on further examination was found to extend into the left atrium.

When the pericardium was opened, this extension could be palpated to extend as a fingerlike process into the lumen of the atrium. It was possible, however, with considerable traction on the two stumps of the pulmonary veins to place a clamp well back on the left atrium, thereby excluding the entire tumor mass. As much of the left atrium as possible was then cut away and the left atrium was closed by a row of mattress sutures and then a running overhand stitch to the edges. A relatively safe and satisfactory closure was thus thought to be established and the pericardium was closed loosely. The chest wall was then closed by approximating the ribs with two No. 28 stainless steel pericostal wires and reconstruction of the soft parts with No. 40 and No. 100 interrupted cotton sutures in layers.

Pathological report: Specimen consists of a piece of tumor tissue invading the pulmonary vein. Quick section shows neoplasm, possibly of mesodermal origin. Additional tissue received is a hilar node which on quick section fails to reveal neoplasm. Additional tissue received is a lymph node from the internal mammary chain of nodes. Quick section shows only lymph node (Fig. 1).

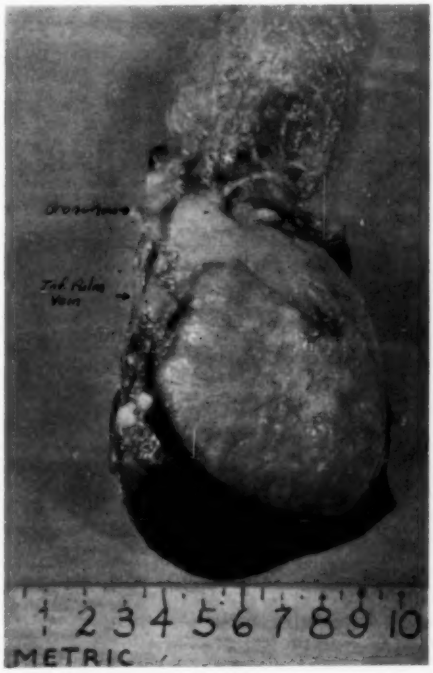

Fig. 2.

The principal specimen consists of a left lung. The bronchus reveals tumor tissue to be present in the lu-

men. The pulmonary vein also shows tumor in its lumen. On sectioning of the lung, there is a firm gray-white mass measuring 7 cm. across the lower lobe. The upper lobe is aerated. Another specimen received consists of a segment of the pulmonary vein at its entrance into the right atrium. Jutting from this segment of vein is a smooth white tumor mass measuring 22 mm. in diameter (Fig. 2).

The microscopic sections show a well-differentiated mesenchymal neoplasm. This is characterized by a cellular tumor in which the cell outlines are indistinct. The nuclei are large, pale, with prominent nucleoli. These cells are situated in bundles and have a fasciculated pattern. There are numerous cells having a blunt cellular cytoplasm and some with a straplike cytoplasm. The neoplasm is well vascularized and it is deeply infiltrated by mononuclear cells. With a Masson differential strain the true characterization of the neoplasm is shown to be a leiomyosarcoma of low grade.

Additional sections show the tumor to invade the bronchus and at this point the neoplasm is ulcerated. This area is deeply infiltrated by acute inflammatory cells. Another section reveals the tumor within the lumen of the pulmonary veins and jutting into the right atrium. A second inspection of the lymph nodes fails to reveal any evidence of metastatic malignancy.

Final pathological diagnosis of left lung: Leiomyosarcoma grade I with extension into the pulmonary vein and the left main stem bronchus.

The postoperative course was uneventful. The patient has returned for periodic follow-up examinations, the last being on Jan. 16, 1952, at which time no particular abnormality was noted. X-ray of the chest Feb. 1, 1952, was negative; no signs of the tumor were present; there were no abnormal findings. She has gained 8 pounds of weight. Her appetite is good. She runs, plays, and attends school regularly. She has no complaints.

COMMENT

The case described represents the first of primary pulmonary leiomyosarcoma reported in a child. The unusual operative procedure necessary for the removal of the neoplasm is noteworthy. We are unable to determine definitely if this tumor is primary in the lung or the bronchus. We believe it is of pulmonary origin due to its presence in the left pulmonary vein and because the mass of the tumor is extrabronchial. The child is alive and well without complaints two years after surgery and three years after onset of symptoms.

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CONGENITAL ABSENCE OF THE SPLEEN

First Lieutenant Norman N. Adler and
First Lieutenant Ellis J. Van Slyke,
Medical Corps, United States Army

CONGENITAL absence of the spleen is rare. Only twelve cases have been reported in the United States and some fifteen cases elsewhere. A review of the literature and presentation of the eighth, ninth, tenth, and eleventh cases appear in a recent article by Polhemus and Schafer.[1] While the anomaly is not fatal in itself, the frequent association with other anomalies such as atrioventricularis and situs inversus has been pointed out.[2, 3, 4, 5]

CASE REPORT

D. L. W., a white male, was born on June 17, 1952, and admitted to the newborn nursery at the U. S. Army Hospital, Fort Eustis, Va.

The family history is negative for heart disease or other congenital anomalies. A sibling, 4½ years old, is alive and well.

The mother is 24 years old, para i, gravida ii, and in 1948 had a cesarean section for contracted pelvis. Her last menstrual period of this pregnancy was Sept. 12, 1951. The mother denies any rashes or serious illnesses during the first trimester of this pregnancy.

The patient was born by cesarean section and had spontaneous respirations and cry. His color was good and he was taken to the newborn nursery immediately after birth. Birth weight was 7 pounds 3 ounces. At this time mild cyanosis of the fingernail beds, lips, and mucous membrane was noted. The infant was suctioned with resulting improvement in color. The patient was given oxygen for the next eight to twelve hours. He continued to have intermittent attacks of cyanosis despite the use of oxygen and suction. The cry was not high pitched nor was there any evidence of spasticity, convulsions, or other signs to suggest intracranial hemorrhage.

Physical examination at this time was essentially negative. The heart and lungs were considered normal.

The baby improved rapidly thereafter and was removed from oxygen on the fourth hospital day. At that time his color was good; he was taking his formula well and was beginning to regain his birth weight. X-ray of the chest was reported as normal.

Just prior to the baby's discharge on the seventh hospital day, he again began to show evidence of very mild peripheral cyanosis. Eight days after discharge he was readmitted to the pediatric ward of the U. S. Army Hospital, Fort Eustis, Va.

He had taken his feedings well at home until the night prior to the day of admission. The patient was noted to be "blue and stiff." There was no evidence of respiratory difficulty and the attack was interrupted when the patient was spanked by his parents and he began to cry. Through the night, the patient had intermittent attacks of cyanosis never lasting more than one or two minutes.

Physical examination showed cyanosis of the entire body, most marked in the area above the lower costal margins. There was slight improvement in color noted with crying and after the patient was put in an oxygen tent. The lungs were clear on auscultation and percussion. The heart was not enlarged to percussion—the rate was rapid but regular. No murmurs or thrills were noted. The skin showed mottled cyanosis and cyanosis of the nail beds, mucous membranes, and lips.

Throughout the next two hospital days, the patient exhibited intermittent attacks of cyanosis even while in

the oxygen tent. Physical examination was considered essentially normal except for the cyanosis. At no time was respiratory embarrassment noted nor any abnormal neurological signs elicited.

On the evening of the third hospital day, the baby vomited several times. The depth of cyanosis became more pronounced in the upper portion of the baby's body and his upper extremities. No evidence of convulsion or spasticity was noted, auscultation of the lungs was normal, and the patient's temperature remained normal.

The rest of the patient's hospital stay was uncomplicated. He continued to have moderate cyanosis which increased whenever he was taken out of the oxygen tent for feedings. His temperature varied from 96° to 99.4° F. rectally, despite all efforts to maintain a constant temperature. On the morning of his twelfth hospital day he was found dead in his crib.

Laboratory studies:

	July 1, 1952	*July 5, 1952*
W.B.C.	24,600	8,100
Neutrophils	63%	58%
Stabs	3%	3%
Lympheytes	32%	34%
Monocytes	2%	3%
Eosinophils		2%
R.B.C.	5,400,000	4,400,000
Hemoglobin	17 grams	15 grams

July 2, 1952. X-ray of the chest: impression, normal. Thoracic spine: abnormal flaring of T-9, T-10, T-11, and T-12. Impression: spina bifida of T-9 through T-12.

On July 9, 1952, a fluoroscopy and barium swallow was considered normal by the x-ray department. Electrocardiograph done on July 10, 1952, reported: Rhythm is regular. Axis deviation is normal. Auricular rate, 176. P-R interval, 0.12. QRS interval 0.06. Q-T interval, 0.24. QRS complex, normal. T waves, normal. RST segment, normal. Precordial leads, normal. Impression: normal electrocardiogram for an infant.

The essential findings on autopsy five hours after death were as follows:

Thoracic contents: Moderate enlargement of the thymus gland was seen on opening the thorax. There were no pleural adhesions or fluid. The heart lay in its normal position with the apex directed to the left and posteriorly; the aorta lay on the right anteriorly in its ascending portion, and descended on the left. No pulmonary artery was readily seen.

Lungs: The lungs were well aerated and not congested. They weighed together 60 grams. The left lung was a mirror image of the right lung, there being a left middle lobe formed by a tissue with the left lower lobe. The trachea and bronchi were normal in appearance.

Heart: The heart was normal in size, weighing 20 grams. It consisted of a common auricle with a band of tissue traversing it, and a common ventricle. The vena cava entered the auricle. The auriculoventricular valve contained two leaflets. The right wall of the ventricle was thin and flabby, the left, thick and firm. There was no interventricular septum, rudimentary or otherwise, nor was there a pulmonary valve or infundibulum. The pulmonary artery started as a blind sac, and its lumen was only 2 mm. in diameter at the origin, gradually increasing in caliber. The aorta was normal in size. The aortic valve contained three cusps, but only one coronary artery was present originating at the only ostium behind the anterior cusp. The course of this artery was roughly that of the normal circumflex artery, sending numerous branches toward the apex around the entire circumference of the common ventricle.

A tortuous, widely patent ductus arteriosus connected the aorta with the stenotic pulmonary artery just below the origins of the innominate artery and the right and left pulmonary arteries, respectively. There was no evidence of thrombosis or any other occlusive process in the ductus arteriosus.

Abdominal contents: The ligamentum teres lay in the midline. The liver was enlarged, weighing 210 grams, and filled the entire upper abdomen. The

left lobe was equal in size and similar in shape to the right lobe. The gall bladder lay just to the right of the midline on the posterior surface of the right lobe. There was no anomaly of the pancreato-biliary tracts. Grossly, the liver substance was normal.

No spleen or splenunculi were present, the ala of the left lobe of the liver occupying the position of the normal spleen. The tail of the pancreas was more readily mobile than normal.

The stomach and intestines were in normal position. No malrotation or anomaly of the mesentery was seen.

The kidneys were normal in size, shape, and position, except for the presence of fetal lobulation of their surfaces. The remainder of the genitourinary tract was normal. The testes lay in the inguinal canals. The adrenals, likewise, were normal in size, shape, and position.

The abdominal aorta descended normally on the left, the vena cava on the right.

Pathological diagnosis:

I. Congenital heart disease.
   - A. Persistent atrioventricularis communis.
   - B. Atresia, pulmonary valve.
   - C. Stenosis, pulmonary artery.
   - D. Patent ductus ateriosus.
   - E. Solitary coronary artery.

II. Congenital absence of spleen.

III. Situs inversus, liver, partial.

IV. Accessory lobe, left lung.

DISCUSSION AND SUMMARY

A case of congenital absence of the spleen with associated cor biloculare, partial situs inversus, and spina bifida has been presented. We wish to note that in all of the previous reported cases a heart murmur was audible, while in our case a cardiac murmur was not heard by any of the several examiners.

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CHONDRODYSTROPHIA CALCIFICANS CONGENITA

CAPTAIN BEDFORD H. BERREY* AND CAPTAIN CECIL H. KIMBALL,**
MEDICAL CORPS, UNITED STATES ARMY, DENVER, COLO.

CHONDRODYSTROPHIA calcificans Congenita is a rare disease occurring in infancy and diagnosed with certainty only by roentgenograms.

This dystrophic process has recently been reviewed by Savignac[1] who found twenty-two previously reported cases in the literature and added one case of his own. Others probably have been reported under different descriptive terms.

Haynes and Wangner[2] noted the following names given to what is probably the same process: chondrodysplasia congenita calcificans, chondroangiopathia calcerea congenita, chondrodystrophia punctata, and chondroangiopathia calcerea seu punctata, the term they used to describe their case.

Recently a newborn infant was observed to have this condition and is reported to add the twenty-fourth case.

A 5 pound 6¾ ounce female infant was the first-born child of a 21-year-old white mother. The pregnancy, except for salpingitis in the early months, was uncomplicated. Delivery was accomplished with low forceps under saddle-block anesthesia (2.5 mg. heavy Nupercaine) supplemented by Demerol 100 mg. and Scopolamine hydrobromide 1/150 grain. Immediately upon delivery the infant was noted to be lethargic with a poor weak cry; mongoloid facies were described by the obstetrician.

The infant measured 17 inches in length, the chest 12½ inches, head 13½ inches, with a crown-rump distance of 12 inches, all felt to be below the expected averages for this weight.

Initially mongolism was suspected; however, further detailed examinations made a diagnosis of achondroplasia or chondrodystrophy more tenable. The possibility of mongolism still exists and the roentgenograms of the skull did reveal upward and outward slanting of the orbits which has been described in cases of mongolism. The infant had a "pug nose" appearance with apparent absence of the nasal bones; a definite saddle nose was present. The palpebral fissures were narrowed and

Fig. 1.—Front view showing depressed nasal bone, spadelike hands, narrowed palpebral fissures, and slanting epicanthal folds.

*Chief, Pediatric Service, Medical Services, Fitzsimons Army Hospital.

**Resident, Radiology Service, Fitzsimons Army Hospital.

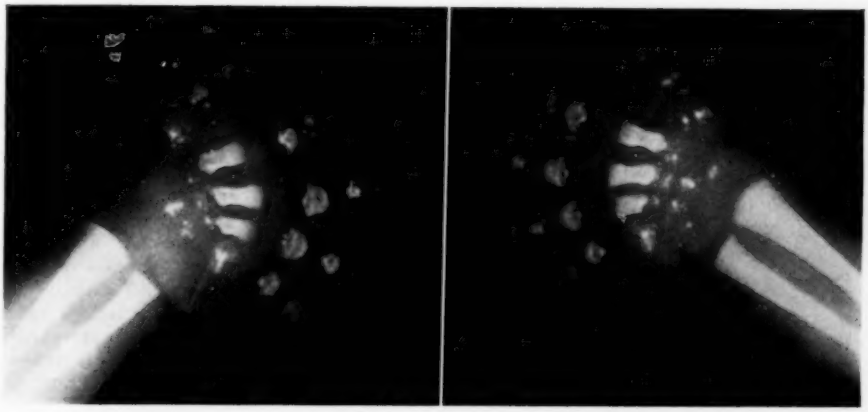

Fig. 2.—Roentgenograms of the hands showing irregular calcium deposits in the epiphyses. Some of the phalanges and metacarpals are formed entirely of irregular calcifications.

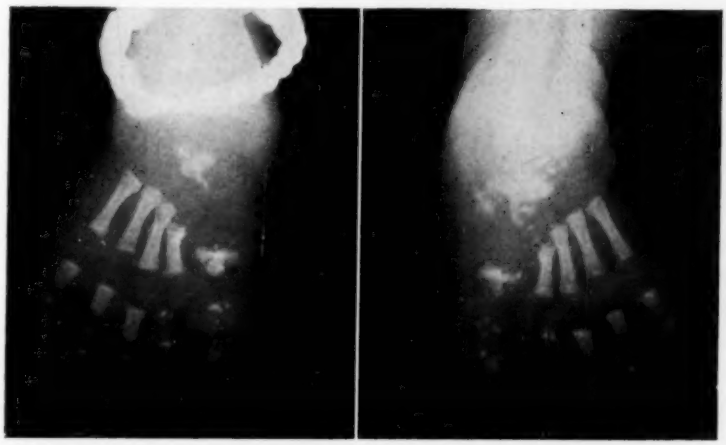

Fig. 3.—Roentgenograms of the feet and ankles showing same changes as noted in Fig. 2.

slanting. A large thick protruding tongue was readily evident. The heart and lungs were considered normal. The liver was palpable 1½ cm. below the right costal margin. The anterior fontanel was small, measuring approximately 1 × 1 cm. A most striking feature was the very short thick "spadelike" hands and extremely

Fig. 4.—Roentgenograms of lower extremities. Note difference in length of femurs (0.5 cm. greater on right side) and increased length of fibulas and stippled calcifications in lower spine and proximal end of femurs.

small fingers (Fig. 1). The toes were much the same, the third toe extending beyond the great toe bilaterally. Moderate stiffness of the hips was noted including slight limitation of abduction. An unevenness of the gluteal folds was noted together with apparent shortening of the left leg, raising the question of congenital dislocation of the hip.

The eyes were examined by the ophthalmologist and no abnormalities were apparent in the lens, vitreous, or fundi.

Roentgenograms were taken when the baby was 36 hours of age. The typical flecklike appearance of calcium deposition in the hands and feet are noted in Figs. 2 and 3. The fibular length was noted to exceed the length of the tibia. A "knobby" appearance noted at the ends of the humerus and ulna was considered suggestive of achondroplasia, and moderate flaring of the epiphyseal ends of the femur and tibia was noted (Fig. 4). The question of congenital dysplasia of the hip has not been definitely confirmed although there is an apparent increase in the distance between the acetabulum and the head of the femur on that side (Fig. 4). The calcification flecking abnormality was likewise noted along the vertebral column. Skull films reveal some degree of nasal shortening, a brachycephalic appearance and slight patency of the anterior fontanel. Deposition of lime salts was observed in the region of the hyoid bone (Fig. 5).

DISCUSSION

Chondrodystrophia calcificans congenita is considered by Caffey[3] under the general heading of congenital cartilaginous dystrophies. However, its exact position in the table of chondrodystrophia has not been finally determined. Any bone with its precursor in cartilage may be involved and frequently is affected. He attempts to distinguish between the spotty and irregular mineralization of the epiphyseal cartilages and round bones of classic achondroplasts and the irregular epiphyseal mineralization of infants and children who are not achondroplastic. He feels that this latter condition is unrelated to achondroplasia and offers a better prognosis without residual deformities or shortened stature.

The pathology of chondrodystrophy has been thoroughly discussed by Potter[4] in her new text. She does not mention chondrodystrophia calcificans congenita as a form of chondrodystrophy.

The diagnosis in this condition is one which can accurately be made only radiologically. The general appearance of the infant suggests a dystrophic process involving bone and/or cartilage.

Savignac[1] notes, "The three terms used in the name of the disease are well illustrated, namely: chondrodystrophy in the shafts of the long bones; calcifications throughout the cartilages, and the congenital character of the condition." These characteristics are well illustrated in our case.

It represents the twenty-fourth instance to be reported, although others may have been reported under different names.

It must be considered a dystrophy of bones having their origin in cartilage and involving the epiphyseal ends of long bones with stippled calcium deposits; other bones where cartilage is a precursor may similarly be involved. It is particularly notable in the epiphyseal centers of the small bones of the hands and feet. Chondrodystrophic changes in the long bones are noted and often the fibular length exceeds that of the tibia.

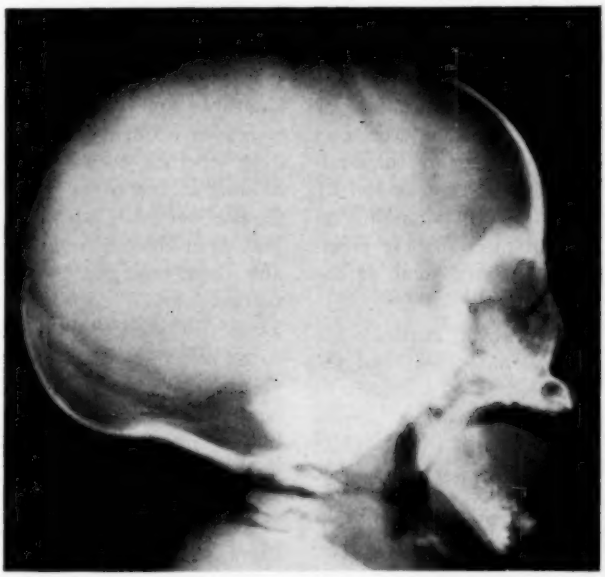

Fig. 5.—Roentgenogram of skull showing depressed nasal bones and calcified hyoid bone.

SUMMARY

A case of chondrodystrophia calcificans congenita is presented with roentgenographic and photographic evidence.

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Medical Progress

CHOICE OF AN ANTIBIOTIC

An Interpretative Review

Samuel Karelitz, M.D.
New York, N. Y.

IN THIS discussion of antibiotics an attempt will be made to present the subject as it occurs to one who is primarily occupied with the care of patients. This neither is, nor is meant to be, an exhaustive review of the immense problem of antibiotics. I shall try to indicate what motivates one in ordering an antibiotic, what decides which and how much to give, and how to give it. The important questions of bacterial resistance and toxicity, and the rationale of the use of combinations of antibiotics will be followed by a section on the current thoughts on the choice of antibiotics for the treatment and prophylaxis of some of the more common diseases.

In this antibiotic era of medicine the antibiotics and sulfonamides head the list of all drugs in the treatment of febrile illness and infection. Penicillin, streptomycin, and the so-called broad spectrum antibiotics, Aureomycin, Chloromycetin, and Terramycin are most commonly used. New antibiotics are being developed constantly. Indeed erythromycin has just been released for general use. The antibiotics have become a great factor in the national economy.[1]

When a patient is first seen with a febrile illness the indications for antibiotic therapy are about as obvious as the disease itself. If the condition is evident, such as scarlet fever, mumps, or measles, the therapy is reasonably well established. If, however, the diagnosis and the bacteriology of the condition are not so clear, the decision to treat the patient with an antibiotic is influenced by many other factors. If the child appears very ill or toxic, or if the fever is high, an antibiotic is rarely withheld. The physician who does not employ antibiotic therapy under these conditions does so with considerable concern. If the condition is an upper respiratory infection he wonders whether he is justified in withholding a drug which might avoid otitis media, cervical adenitis, pneumonia, etc., even though he knows he will be able to successfully treat these complications should they arise. Since a hemolytic streptococcus may be the cause of the infection, nephritis or rheumatic fever might be avoided if he treats the patient early with antibiotics or sulfonamides. Can he permit the patient to develop meningitis or some other serious complication because of postponement of antibiotic therapy?

The omission of antibiotics or sulfonamides often requires a long and detailed explanation to the parents that there are definite and specific indications for the use of antibiotics; that these drugs may be harmful, and that drug resistance is becoming a more serious problem. These and other cogent arguments are often of no avail. Laymen feel confident that new drugs will be discovered to combat the ever-increasing number of re-

From the Mount Sinai Hospital and the Willard Parker Hospital.

sistant bacterial strains. They are interested only in the immediate welfare of their child. Newspaper, radio, and magazine articles, and intensive advertising of the pharmaceutical companies about the "miracles" produced by antibiotics are more convincing to parents than any argument brought forth by the pediatrician. Even the consultant is questioned about the wisdom of withholding antibiotic or sulfonamide therapy in presence of an infection. Occasionally no amount of discussion can convince a determined parent that the "penicillin shot" will not alter the course of the particular infection. "He seems to need it and always responds promptly to the penicillin shot." In such circumstances a second physician may be called if the first does not yield to the parents' wish for an antibiotic. The pressure to order antibiotics is obviously so great that they are given when needed and often without indication.

It is indeed fortunate that antibiotics have never been sold without a doctor's prescription. Uncontrolled sales of these agents would result in many more instances of toxicity, and in all probability many more resistant strains of bacteria.

The excessive and indiscriminate use of antibiotics is by no means limited to practitioners. In the hospital antibiotics are often prescribed without knowledge of the bacterial etiology of the infection and the suitability of the antibiotic prescribed. Omission of an antibiotic in the treatment of a new patient is considered a less desirable practice by some of the house staff and by some of the attending pediatricians than is the administration of at least one, and often two or more, drugs immediately upon admission to the hospital. It is considered necessary to "cover all possibilities."

The extent to which antibiotics are ordered in a children's hospital can be surmised from the survey made on the pediatric wards of the Mount Sinai Hospital of New York City on July 29, 1952. Of forty-five patients antibiotics were correctly chosen and administered in suitable dosage to twenty-two, or about half of the patients, and excessive amounts were given in fifteen instances. Moreover, antibiotics were administered to five patients suffering from diseases unaffected by these drugs. Three failed to receive antibiotic therapy although these drugs seemed to be indicated.

To attain a more rational and judicious use of antibiotics requires an intensive and persistent effort at reorientation and re-education of both the lay and professional public.

Let us return to the sick patient. Having decided that the patient has an infection, specific or otherwise, which should not be permitted to run its course without antibiotic or sulfonamide therapy, what are the criteria by which one determines which shall be selected, how much should be given, and by what route?

Since the most common reason for being called to a home to see a sick child is an upper respiratory infection, let us first review how one arrives at suitable therapy for this condition. Within a few moments after examining the child one must evaluate the infection as to its possible etiology. Since the precise etiology of the infection cannot be determined without laboratory aid, the presence or absence of exudate, edema, and degree of distribution of redness in the pharynx may be helpful. Knowledge of the

nature of the more prevalent types of upper respiratory infections in the vicinity of one's practice at the particular time or season may be helpful. Previous experience with other patients with similar findings who did or did not recover spontaneously within a few days, or who failed to respond to penicillin or some other drug, may be of assistance. Discussion of this matter with other physicians in the community who have had experience with similar conditions is often of the greatest value.

The same type of analysis may be invoked in any and all other infections. In general, however, the choice of an antibiotic is made after a rapid but systematic evaluation of the clinical pattern of the illness and a review of the knowledge of antibiotics as it pertains to the particular problem in question. Such an evaluation can be reduced to the answers of the following considerations.

CRITERIA FOR CHOICE OF ANTIBIOTIC

1. Which are the bacteria that most commonly produce the type of infection in question?
2. To which antibiotic are these organisms usually most susceptible?
3. Are the bacteria causing the infection easily accessible to the chosen antibiotic in adequate concentration?
4. Is the antibiotic effective when taken orally?
5. How does the patient's previous experience with antibiotics aid in the choice of therapy?
6. How does the economic factor influence antibiotic therapy?

DISCUSSION OF CRITERIA

1 and 2. *Which are the bacteria that commonly produce this type of infection, and to which antibiotic are these organisms most susceptible?*

A careful physical examination and an adequate history usually enables one to decide whether the infection is upper respiratory, pulmonary, gastrointestinal, or whether it involves some other part of the body. Once the site of infection is determined the bacteria most commonly involved are known. The most effective antibiotic for these bacteria is the one to select.

In the case of otitis media a hemolytic streptococcus, a *Staphylococcus aureus*, or a pneumococcus are by far the most common agents involved. Penicillin is the drug of choice against any and all three cocci, although Aureomycin, and possibly erythromycin may be preferable for some strains of staphylococci.

When time permits, a white blood cell count and a urine analysis may be of further aid in selecting an antibiotic. A high white cell count with a relative polynucleosis indicates a pyogenic type of bacteria and usually requires the use of penicillin alone or with Aureomycin in some conditions such as pneumonia in infants less than one year of age. A high white blood cell count with a relative lymphocytosis in a child who is coughing may suggest pertussis and indicates need for one of the broad spectrum antibiotics. Leukopenia with normal distribution of cells or a predominence of lymphocytes might suggest an infection with a gram-negative bacillus and calls for an antibiotic effective against such organisms. Under other circumstances such a blood count might lead to a diagnosis of a viral infection as influenza or roseola infantum which do not respond to antibiotics.

Evidence of glomerular nephritis points to a recent infection with a beta hemolytic streptococcus, and may be considered as a definite indication for penicillin therapy. Evidence of lipoid nephrosis, especially if associated with septicemia, peritonitis, or skin infection, commonly implicates a pneumococcus or a streptococcus which should be treated with penicillin.

Pyuria when first observed is commonly caused by infection with a colon bacillus, a staphylococcus, or a streptococcus. If pyuria continues after an adequate course of therapy with the usual antibiotics, the possibility of an infection caused by *Pseudomonas aeruginosa (pyocyaneus), B. proteus,* an enterococcus, or a resistant staphylococcus, or some unusual bacteria must be entertained, and the use of one of the more toxic antibiotics may have to be considered.

3. *The next consideration is whether the site of infection is easily accessible to the chosen antibiotic in adequate concentration, and in what form and dosage this antibiotic should be given to attain a lasting therapeutic level.*

An antibiotic must reach a focus of infection in adequate concentration to be effective. Obviously the antibiotic would have to be excreted by the kidney to influence a urinary tract infection. Likewise, if the case was one of meningitis a drug which passes more readily through the choroid plexus may be superior and preferable. Although some antibiotics are more effective against *Hemophilus influenzae,* sulfadiazine is added to the treatment because of its ability to reach the spinal canal more readily. Likewise it has been reported that Neo-Penil, one of the newer penicillins, more readily enters the subarachnoid space than do other forms of penicillin.

Neo-Penil[2] c. diethylaminoethyl ester hydriodide (S.K.F.) is also said to concentrate in the lungs and bronchi in greater amounts than do other forms of penicillin. Clinical advantage of this form of penicillin in pulmonary and bronchial disease has already been suggested.[3]

An abscess or osteomyelitis[4, 5, 6] require large doses of antibiotics for a long time, since with usual dosage the concentration of the antibiotic which reach such foci is relatively low. In osteomyelitis it may be necessary to give two or three times the usual dose of antibiotics for three to six weeks after the blood culture is sterile and the temperature becomes normal, unless external drainage is established.

To attain lasting adequate systemic concentrations of penicillin it is necessary to administer a penicillin which is slowly excreted from the body, or one which is slowly absorbed from the intramuscular space, or to inject large doses of aqueous penicillin at frequent intervals even though it is rapidly absorbed and rapidly excreted.

Lasting high concentrations of penicillin were first accomplished by administering large doses of the aqueous salt of penicillin every two to three hours. It was then discovered that Caronamide[7] or Benemid[8] compete with penicillin for excretion by the renal tubules. The loss of penicillin is thereby retarded, resulting in higher blood levels for a longer time. This was followed by an attempt to slow the absorption of penicillin by blending it with beeswax,[9] sesame oil, and aluminum monosterate. Although successful, these preparations have been largely replaced by the relatively less

soluble forms of crystalline penicillin.

Crystalline aqueous procaine penicillin, when injected intramuscularly, is absorbed slowly enough to maintain high blood and tissue levels. If given in large doses therapeutic blood levels appear rapidly in one to two hours and in most patients adequate levels are maintained for twelve to twenty-four hours, sometimes longer.

Procaine penicillin G is now commercially available in concentrations of 300,000, 600,000, 800,000, and 1,000,000 U. per milliliter. These preparations result in higher systemic concentrations and are indicated in more serious infections or when more resistant bacteria are present.

Bicillin[10] (Benzethacil), N.N′ dibenzylethylenediamine dipenicillin G, a more recent contribution to the family of penicillin preparations, is absorbed more slowly than are other forms of crystalline penicillin now available. A single intramuscular dose of 1,200,000 units results in blood levels up to 0.2 μg per milliliter within one to two hours, and 0.02 to 0.04 μg for as long as seven to fourteen days and longer in the majority of cases. Higher levels can be obtained with larger doses. Its availability is a boon to penicillin therapy, and more especially in prophylaxis, e.g., rheumatic fever.

In the case of the broad spectrum antibiotics and streptomycin higher blood levels may be maintained for longer periods by merely increasing the dosage.

4. *Is the antibiotic effective when taken orally?*

Penicillin, Aureomycin,[11] Terramycin, Chloromycetin, and erythromycin are readily absorbed and may be given orally. They reach their maximum blood levels in about one to two hours. Most of the aqueous penicillin is excreted in three to four hours, and it takes six to eight hours before most of the broad spectrum antibiotics are excreted. Aureomycin, Terramycin, and Chloromycetin are given parenterally only when high blood concentrations are urgently needed, when the patient is too sick for oral therapy, or if the patient cannot tolerate them because of the vomiting or diarrhea which they often produce. Since little streptomycin or dihydrostreptomycin, polymyxin, bacitracin, or neomycin are absorbed from the gastrointestinal tract, they are given intramuscularly except for local action in the intestinal tract. In the case of penicillin there is an increasing tendency to treat all diseases by the oral route[12, 13] except for the very severe conditions such as subacute bacterial endocarditis, osteomyelitis, meningitis, or peritonitis which require sustained high levels that can be more readily and more regularly obtained by parenteral therapy. While penicillin taken by mouth is usually effective, the results are more consistent when it is injected.

Antibiotics are poorly absorbed from the rectum.[14, 15, 16] This route should not be used except when another pathway is not available.

5. *How does the patient's previous experience with antibiotics aid the choice of therapy?*

Any one of the antibiotics might be tried if the patient has never undergone treatment with it previously, or if he has received it previously without ill effect.

If a patient has previously manifested allergy to penicillin, another

antibiotic should be chosen unless penicillin is urgently needed, and no other therapy will suffice. Then, penicillin O[17] might be tried or penicillin O or G might be administered along with an antihistaminic. A history of a severe gastrointestinal reaction to Aureomycin or Terramycin would suggest the use of smaller doses in a suitable vehicle, or that some other antibiotic be employed. If a patient has had Chloromycetin it should not be repeated within a few months unless there is good reason to believe that another therapeutic agent will be ineffective.

6. *How does the economic factor influence the choice of an antibiotic?*

Assuming that two or more antibiotics are equally effective, and one is no more toxic than the other, the cost of medication may determine the choice of antibiotic. An important factor in the economy of therapy is the judicious use of antibiotics. They are frequently given for illnesses which are not amenable to antibiotic therapy. Excessive amounts are given when much smaller doses would suffice, and might be more effective. If antibiotics are indicated at all they should be given in adequate dosage for a reasonable period, usually for at least two or three days, before changing to another drug. Often one antibiotic is discontinued and a second started, or a second is added to the one originally chosen after only twenty-four hours of treatment. Such a short period may not be sufficient to permit the benefit of the course of therapy undertaken to become evident. Such needless purchases of additional antibiotics cause unnecessary expense to the patient's family.

An additional consideration in antibiotic therapy is the question of antibiotic blood levels and bacterial susceptibility or resistance to these drugs. The blood level of an antibiotic at a given moment does not indicate the concentration at the site of infection.[18] Furthermore the same dose of antibiotic administered to several individuals may produce quite different levels.

Since blood levels of antibiotics do not necessarily parallel their clinical effect,[19] the latter is considered to be a more reliable index of the progress of therapy. Furthermore, determination of a blood level is of little significance unless the etiological agent and its bacterial resistance pattern are known. Since cultures are frequently not made in practice there is little indication for blood level determinations.

In hospital practice an attempt to determine the bacterial etiology of an infection is usually made on admission of the patient. Since illness encountered in hospitals is likely to be more serious and of longer duration, and since the patient has often been treated with an antibiotic before admission to the hospital bacterial resistance is more frequently observed. In such cases knowledge of the blood level may aid the therapist in choosing the most suitable dosage of the antibiotic.

Failure to control infection with large doses of antibiotics even when high blood levels are obtained usually indicates bacterial resistance.

Occasionally determination of the concentration of an antibiotic in the blood in conjunction with a knowledge of the susceptibility of the bacterium causing the infection may bring to light a situation which cannot be controlled with the therapeutic regi-

men in use. For example, a *Spirillum minus* isolated from the blood of a patient was found to be resistant to 200 U. of penicillin per milliliter, a level very difficult to maintain over a long period. Very large doses of penicillin (250,000 units of the aqueous solution) were injected intramuscularly every three hours without improvement. Although this spirillum was sensitive in vitro to ordinary and easily attained levels of streptomycin and Aureomycin, 2 Gm. daily of streptomycin failed to control the infection. Aureomycin, 2 Gm. daily, promptly cured the child of an infection he had had for almost four years.

BACTERIAL RESISTANCE TO ANTIBIOTICS

The steady increase of bacterial resistance to the various antibiotics is growing in significance. While it has not seriously affected the clinical results, instances of failures in therapy are more numerous. The resistance of the gonococcus to sulfonamides has altered their usefulness in the prophylaxis and treatment of gonococcal infection. The widespread use of sulfonamides in prophylaxis of hemolytic streptococcal disease[20] has also resulted in the emergence of resistant strains of this organism, but has not greatly interfered with the over-all effect of the sulfonamides. The rapid development of resistance of *Mycobacterium tuberculosis* to streptomycin and dihydrostreptomycin is a common observation. Transmission of resistant strains has been observed.[21]

More important clinically is the increasing number of strains of *Staphylococcus aureus* (penicillinase producers) found to be resistant to penicillin.[22, 23, 24, 25] This is particularly true in hospital wards, nurseries, and in institutions where *Staph. aureus* infection is prevalent. Usually the hospital personnel contract the resistant strains from patients and infect other patients, but some patients unsuccessfully treated at home arrive with resistant bacteria. In outpatient departments, in offices, and in factories the incidence of penicillin-resistant *Staph. aureus* was found to be about 3 to 12 per cent of the individuals harboring *Staph. aureus*. In some hospital wards the incidence of penicillin-resistant *Staph. aureus* has increased in a year or two from 25 to 35 per cent to as many as 50 to 60 per cent.

Penicillin-resistant strains seem to emerge when bacteriostatic rather than bactericidal doses are employed. The amount given should always be large enough to destroy the bacteria rapidly and completely.

Bacterial resistance may also be due to the emergence of bacterial mutations[26, 27] which may be of entirely different resistance pattern than the parent bacteria.

Schneierson[28] has shown an increasing resistance of *E. coli*, *B. proteus*, *Staph. aureus*, and *S. fecalis* to Aureomycin, and of *E. coli*, *Ps. aeruginosa*, and *B. proteus* to chloramphenicol. The findings with Aureomycin are probably equally true of Terramycin, since, with rare exception, the natural and acquired resistance of most bacteria to Terramycin closely parallels that to Aureomycin. Herrell and associates[29] have shown that strains of *E. coli* made resistant to Aureomycin, Terramycin, or to Chloromycetin regularly show an increased resistance to all three but not to streptomycin. If made resistant to streptomycin, these bacteria are not resistant to the three

broad spectrum antibiotics. While these observations need not be applicable in actual practice the clinical implication of these observations is that in presence of a growing resistance to Aureomycin, for example, a better result might be had by the introduction of streptomycin, but not by the addition or substitution of Terramycin or Chloromycetin.

Monnier and Schoenbach[30] found that if one of the broad spectrum antibiotics is added to the penicillin treatment of a penicillin- resistant strain of *Staph. aureus,* the bacteria lose part or all of their resistance to penicillin. These authors therefore recommended the addition of a broad spectrum antibiotic to the penicillin treatment when such a resistant organism is encountered.

Resistance of the tubercle bacillus to the isonicotinic acid derivatives is being discussed widely. It is suggested by some that these drugs be used in conjunction with streptomycin and para-aminosalicylic acid in the treatment of tuberculous meningitis.

SIMULTANEOUS USE OF MORE THAN ONE ANTIBIOTIC

It has been shown experimentally by Price and co-workers,[31] Spicer,[32] Jawetz, and others[33, 34, 35, 36] that when combinations of antibiotics are used for specific organisms the results may be variable. The response is either indifferent, that is, there is neither increased nor decreased action; the action is increased either through synergism of the drugs or through an additive effect; or there is decreased action due to interference or antagonism between the drugs.

They[33] also demonstrated that this phenomenon of antagonism is observed only when a relatively ineffective concentration of one drug is added to a therapeutically effective concentration of another. Jawetz and associates further demonstrated that this antagonism which occurs between penicillin and Aureomycin, or Terramycin, or Chloromycetin disappears if therapeutically effective doses of both antibiotics are employed simultaneously. It is believed that this antagonism is the result of the retardation of bacterial growth by the broad spectrum antibiotics, thus rendering the penicillin less effective.

Jawetz and Gunnison[35] offer a tentative scheme of grouping of the antibiotics: Group I, consisting of penicillin, streptomycin, bacitracin, and neomycin are frequently synergistic with each other, occasionally indifferent, never antagonistic. Group II, consisting of Aureomycin, Chloromycetin, and Terramycin, and possibly the sulfonamides are neither synergistic with, nor antagonistic to, each other but simply additive in their effect as might be expected from an increased dose of a single one of these drugs.

While these phenomena of antagonism and synergism seem well established in the laboratory, corroborative clinical evidence is still scant and difficult to demonstrate except in rare instance. Eagle and Fleischman[37] has demonstrated synergism between penicillin and bacitracin in the treatment of syphilis. Johnson and Meleney[38] found synergism between penicillin and bacitracin against resistant hemolytic staphylococci. Synergistic action between penicillin and Aureomycin[39] has been demonstrated in penicillin-resistant subacute bacterial endocarditis which has failed to respond to large doses of penicillin alone. Lep-

per and Dowling[40] observed apparent antagonism between penicillin and Aureomycin in the treatment of pneumococcic meningitis. Thus penicillin and Aureomycin were antagonistic in one instance and synergistic in another.

It is thus evident that the phenomena of interference or antagonism and of synergism are demonstrable in vivo as well as in vitro.

Dowling[41] has summarized the possible advantages of combinations of antibiotics as follows: (1) In mixed infections, one antibiotic may be effective against one bacterial species and the second against another, e.g., penicillin and streptomycin in peritonitis. (2) The use of a second antibiotic may prevent the development of a superinfection which might occur if the first were used alone. During streptomycin therapy staphylococcal infections may develop. Dowling therefore suggests the use of a sulfonamide, penicillin, or one of the broad spectrum antibiotics along with streptomycin, especially in children. (3) The side effects which may accompany the use of large amounts of one antibiotic may be prevented by the administration of smaller amounts of two agents. (4) A second antibiotic is employed to prevent or delay the development of resistance to the first, e.g., para-aminosalicylic acid and streptomycin in tuberculous meningitis. (5) There may be true synergism between antibiotics.

Additional reasons for combined antibiotic therapy might be suggested. Combinations are indicated in serious infections of which the exact etiology is not known and delay in treatment might be serious, as in undiagnosed bacterial meningitis or in tracheobronchitis. Combinations of antibiotics or antibiotics and sulfonamides are indicated to hasten the cure of a meningeal infection with an organism against which the drug of choice enters the subarachnoid space slowly and in low concentration. A second effective drug which enters the spinal canal more rapidly is therefore added, e.g., the addition of sulfadiazine to the penicillin treatment of pneumococcus or streptococcus meningitis, or of sulfadiazine to streptomycin or to Chloromycetin in influenzal meningitis, or of Aureomycin to the penicillin treatment of subacute bacterial endocarditis.

Many combinations commonly used could be mentioned. The desire to cover all possibilities in an unidentified infection, or the idea that if one is good two are better, are strong stimulants for this type of treatment. A possible danger exists in this type of therapy, the magnitude of which is still a question.

Until there is further clarification of the problem of the use of combinations of antibiotics, it may be wiser to treat with a bactericidal dose of a single antibiotic and change to or add another only after the first has had an adequate trial. However, combinations of antibiotics may be indicated at the onset of treatment as in the instances cited above. When such conditions exist clinical experience reveals that they may be given without real danger of "interference."

TOXICITY

The toxicity of an antibiotic is an important consideration when deciding which one to order. Penicillin, Aureomycin, and Terramycin are of relatively low toxicity. Chloromycetin, streptomycin, and neomycin are

more likely to be toxic, while polymyxin and bacitracin frequently show evidence of toxicity.

Toxicity may be of a general nature, or as in the case of Chloromycetin, streptomycin, bacitracin, and polymyxin, specific organs or systems may be injured. All antibiotics may produce toxic reactions even when given in therapeutic doses for a short time, but the frequency and severity of toxic reactions are usually related to the size of the dose and the duration of treatment. This is least striking in the case of penicillin, except when it is introduced intrathecally.

In addition to their direct toxic effect antibiotics induce reactions in two other ways: they may elicit allergic reactions in sensitized individuals, and by eliminating predominent bacteria they may pave the way or create fertile ground for invasion by antibiotic-resistant fungi and bacteria.

Of all the antibiotics penicillin is the least toxic. Reactions are primarily of an allergic nature. They occur in approximately 2 to 5 per cent of adults, less frequently in infants and children. Allergic reactions most often involve the skin; urticaria is the most common manifestation but angioneurotic edema and rarely exfoliative dermatitis also occur. Fever, enlargement of the lymph glands, asthma, arthralgia, and joint swelling are encountered. Anaphylaxis[42] has occurred, but proved cases are very rare. Penicillin O was considered to be less allergenic, but it has been shown by Riseman and Boyer[43] and Siegal[44] that penicillin O is no less allergenic than penicillin G. If the reaction to penicillin is mild, and the antibiotic is again indicated even a few days later, it may be tried in small doses at first, alone or with an antihistaminic. The fact that an allergic reaction has occurred does not indicate permanent sensitization in most cases. Usually this sensitization is of a temporary nature and disappears.

Penicillin given intrathecally may be neurotoxic. Amounts up to 10,000 units in 10 c.c. of diluent are usually well tolerated. Larger amounts, 50,000 to 100,000 units, have been given without mishap, but evidence of injury to the central nervous system has occurred with such doses.

Aureomycin, Terramycin,[45] and Chloromycetin are most frequently troublesome because they induce gastrointestinal irritation, nausea, vomiting, and diarrhea. Allergic reactions, skin eruptions, and fever may also occur. These drugs may also have a depressing effect, which often is merely an expression of the ill feeling, the anorexia, and nausea. Nausea and vomiting occur in 5 to 30 per cent after taking Aureomycin, especially when the dose is 40 to 50 mg. per kilogram per day or larger, and is taken for more than one to two days. Although Terramycin is less irritating to the gastrointestinal tract, Smadel[46] found it more so in cases of scrub typhus. Chloromycetin induces these reactions less often.

The gastrointestinal disturbance is often worse than the initial disease for which the antibiotic was given. Diarrhea in some patients[47] persists for weeks and months and is occasionally hemorrhagic, and in rare instance in adults ulcerative colitis is said to have resulted. Perianal and vulval irritation and pruritus are common, and are very annoying. Blacktongue, buccal mucosal, lingual, tonsillar, and gingival ulcerations may develop in as

little as two to four days after treatment with any of the broad spectrum antibiotics and with penicillin. These reactions are usually spontaneously reversible.

Recommendations have recently been made[48] for reduction of the dosage of Aureomycin and Terramycin to 20 to 25 mg. per kilogram per day except in severe infections to avoid unnecessary gastrointestinal irritation, and because they seem to be effective in smaller amounts.

In the past year an ever-increasing number of cases of anemia, in some irreversible aplastic anemia, have been reported.[49, 50] These include children and adults. In almost all instances the anemia developed after the patient had two to three courses of Chloromycetin within a period of several months, or after a single course was continued for a long time. An initial short course of Chloromycetin seems not to produce these serious complications, although reversible anemia has been noted after only seven days of Chloromycetin therapy. Rosenthal[51] has noted in two patients that the effects were detectable first in a drop of platelets followed by a drop in white blood count and granulocytes. In other cases other blood elements may be suppressed first. In most instances there was a gradual depression of all blood elements when the condition was first noticed.

In view of these serious developments it is recommended that Chloromycetin be employed only if other less toxic drugs do not suffice. Chloromycetin should not be given for mild infections which can be treated by other drugs.

If Chloromycetin is selected, frequent and careful blood examinations (twice weekly) should be made and the drug discontinued with the first manifestation of depression of bone marrow activity. Unfortunately an occasional case develops anemia after the drug has been discontinued.

The most common manifestation of toxicity caused by streptomycin is vertigo.[52] Streptomycin and dihydrostreptomycin are very much alike in this respect except that dihydrostreptomycin is said to produce less vertigo, but possibly more hearing disturbance. When given to children in dosage of 1 to 2 Gm. daily for about fourteen days the majority of them develop reversible equilibrium disturbances. Smaller doses or shorter courses are less toxic usually, although reactions have been noted in four to five days in some instances. When given over a period of months, as for tubercular meningitis, eighth nerve damage[53] and deafness of different degrees may develop. Permanent deafness has been noted in 3 to 10 per cent of those recovering from streptomycin-treated tubercular meningitis.[54, 55]

Except in the case of tuberculous meningitis, streptomycin and dihydrostreptomycin rarely need be given intramuscularly for longer than four to seven days. If prolonged therapy is needed other less toxic antibiotics should be selected.

Polymyxin and bacitracin are regularly nephrotoxic but when the dosage is reduced to 2 to 2.5 mg. per kilogram and approximately 50,000 U. daily, respectively, toxic effects are said to be minimal and the clinical effect favorable.

While the more toxic drugs are not to be used generally, situations do occur when it is safer to risk the toxicity of the drug to cure a stubborn and

dangerous infection which fails to respond to the less toxic drugs.

It was previously mentioned that in addition to their toxic action the antibiotics may produce difficulties indirectly by replacement of pathogenic bacteria sensitive to these drugs, with gram-negative bacilli and fungi which are very difficult to eradicate. Monilial infection[56] of the mouth, pharynx, tonsils, and lower respiratory tract and intestines is not an uncommon complication of therapy with these antibiotics. The stubborn infection of the genitourinary tract with resistant bacteria which replace those eradicated has already been mentioned. McCurdy and Neter[57] have observed an invasion of the nasopharynx with gram-negative bacilli after penicillin therapy and even more so following the use of a combination of penicillin with Terramycin or with Aureomycin.

One may question whether the increase in viral disease observed in recent years is due largely to the better techniques for their identification, or whether the elimination or reduction of bacteria by antibiotic and chemotherapeutic drugs may have played a role by removing a barrier against invasion by pathogenic viruses.

In the section which follows antibiotic therapy and prophylaxis of some of the infectious diseases will be discussed. Some of the more important diseases have either been omitted (tuberculosis except for meningitis), or treated very briefly (congenital syphilis, dysentery, brucellosis). In the latter group references have been given to some of the detailed reports on those subjects.

DIPHTHERIA

None of the antibiotics or sulfonamides possess diphtheria antitoxic activity. It is important, therefore, to stress that diphtheria antitoxin be administered promptly after taking the usual precautions for horse serum hypersensitivity whenever diagnosis of diphtheria is seriously considered.

In acute diphtheria a daily dosage of 300,000 to 1,000,000,[58, 59, 60, 61, 62,] and rarely 2,000,000[63] units or more of aqueous procaine penicillin will eradicate *C. diphtheriae* from about 75 per cent of the patients in from twelve hours to several days. Aureomycin,[64] 25 to 50 mg. per kilogram per day, and Terramycin,[65] 25 to 50 mg. per kilogram per day, are also effective, more so in the acute disease than in the diphtheria carriers. Chloromycetin[66] and streptomycin[67] have also been shown to be effective in diphtheria. Other antibiotics[68] are effective in vitro, but there is little or no evidence of their in vivo effect.

Streptomycin 1 Gm. daily eradicated *C. diphtheriae* in three days in one case of diphtheritic pharyngitis and otitis media after treatment with 900,000 units of aqueous procaine penicillin daily for five days, 50 to 100 mg. per kilogram per day of Aureomycin for the next five days, and both together for five consecutive days failed.

Aqueous penicillin administered locally as nose drops, as aerosols, or as troches or chewing gum is occasionally effective in diphtheria carriers but is rarely successful in acute faucial diphtheria. The combination of local and parenteral penicillin affected the elimination of *C. diphtheriae* most rapidly in both carriers and in acute diphtheria.

Treatment with any of the antibiotics should be continued until three consecutive daily nose and throat cultures or wound cultures are negative.

The patient should be removed from contact with other cases of diphtheria or diphtheria carriers as soon as possible to avoid reinfection.

MUMPS

Neither mumps nor its most common complications, orchitis and meningitis or encephalitis, seems to respond to any of the known antibiotics or sulfonamides; however, in cases of complicating suppurative parotitis and other purulent complications, penicillin has been effective.

SCARLET FEVER, STREPTOCOCCAL SORE THROAT WITHOUT AN EXANTHEMA, AND ERYSIPELAS

Scarlet fever, like other infections produced by group A hemolytic streptococci, responds favorably to penicillin,[69, 70] the sulfonamides,[71, 72] and to Aureomycin[73] and Terramycin.[74] Good results in young children are noted with daily intramuscular injections of 300,000 units of aqueous procaine penicillin or multiple daily doses given orally (for example, 150,000 to 200,000[75] units of a buffered preparation given every six to eight hours or three to four times a day for seven, preferably ten days).

Penicillin influences the rash little, if at all, while gamma globulin,[76, 77] convalescent serum, or scarlet fever antitoxin may cause the rash to disappear rapidly. In other respects penicillin is more effective than the antitoxic preparations. Penicillin causes the temperature to become normal in about three days. The suppurative complications are prevented or if present yield to treatment. In most penicillin-treated patients the upper respiratory tract is cleared of beta hemolytic streptococci in from twenty-four to forty-eight hours. Recurrence of the streptococci is more infrequent if treatment is continued for ten days. Recurrent scarlet fever is rarely seen after penicillin treatment. Nonsuppurative complications such as rheumatic fever[78, 79] and nephritis[80] are sharply reduced.

CHICKEN POX[81]

Neither penicillin nor Aureomycin alter chicken pox, but both the antibiotics and sulfonamides are useful in the treatment of such complications as impetigo, erysipelas, etc.

GERMAN MEASLES

This disease is usually so mild that antibiotics or sulfonamides are not indicated except for the relatively uncommon suppurative complications.

MEASLES

The earlier reports[73, 82] of beneficial influence of antibiotics on measles have had to be qualified in the light of more recent studies. Penicillin[83] or Aureomycin have been found useful in the treatment of the bacterial complications of measles. When begun in the pre-eruptive or early eruptive phase of measles, these antibiotics (300,000 units of aqueous procaine penicillin once daily intramuscularly or 50 mg. per kilogram per day of Aureomycin divided into equal doses) bring about cure of the complications already present and prevent further development of pulmonary, otitic, and sinus disease. The temperature becomes normal about two days earlier in the treated cases as compared with the controls. No difference was noted on the rash, photophobia, or cough. In all probabilities other antibiotics and sulfonamides would also be effective, as might be smaller doses of Aureomycin.

All young children with measles should be given antibiotic or sulfonamide treatment as soon as the diagnosis is made and continued until two days after the temperature becomes normal. The prophylactic efficacy of a single injection of Bicillin is now being investigated.

PERTUSSIS

Bacillus *H. pertussis*[84] is quite susceptible in vitro to Aureomycin,[85] Terramycin,[86, 87, 88] and Chloromycetin,[89, 90] as well as to streptomycin[91, 92, 93] and most of all to polymyxin.[94, 95]

In vivo studies have resulted in conflicting reports. While some are enthusiastic about the advantage of Chloromycetin,[89, 90] others find Terramycin[86, 87, 88] or Aureomycin[85] distinctly beneficial and others seem to observe little or no difference between these drugs and untreated controls. Some find a distinct superiority of human convalescent serum, gamma globulin made from hyperimmune serum, or rabbit antibacterial serum over any and all of the antibiotics. The toxicity of polymyxin[95] outweighs its usefulness. Observations made at the Willard Parker Hospital[96] have suggested that in infants penicillin, by its action on secondary bacteria, is lifesaving, but that other antibiotics added to penicillin seemed to exert little or no advantage over those treated with penicillin alone.

Until a more specific drug is found against *H. pertussis* infants ill with the disease should be treated with one of the broad spectrum antibiotics in dosage of 50 mg. per kilogram per day.

The preferred antibiotics are those having the greatest activity against streptococci, staphylococci, and *H. influenzae,* in addition to their effect on *H. pertussis.*

BRUCELLOSIS

Aureomycin,[97] 50 mg. per kilogram per day, or sulfadiazine, 0.2 Gm. per kilogram per day, orally, plus dihydrostreptomycin, 40 mg. per kilogram per day intramuscularly are recommended concurrently for fourteen days in the bacteriemic type, and for four weeks in localized infection. A single priming dose of Aureomycin, 25 mg. per kilogram, is recommended. In chronic brucellosis these drugs are less successful.

DYSENTERY

(a) Shigellosis. Streptomycin,[98] 100 mg. per kilogram per day given orally, or 40 to 50 mg. per kilogram per day of Aureomycin, Terramycin, or Chloromycetin for four to five days is recommended. A single priming dose of 25 mg. per kilogram is recommended. Sulfadiazine is also effective as is Sulfasuxidine and Sulfathalidine. (b) Amebic. Terramycin,[99] Aureomycin,[100] and Chloromycetin[101] are recommended in dosage of 50 mg. per kilogram per day. Treatment for four to six days yields cures in about 75 to 85 per cent. If hepatitis is present, chloroquine should be used concommitantly.

SYPHILIS

Congenital syphilis responds to penicillin.[102, 103, 104, 105] One hundred thousand to 400,000, usually 200,000, units per kilogram are given over a period of ten to fourteen days either in daily doses of aqueous procaine penicillin or in multiple daily doses of penicillin K. Reversal of serology is observed in three to six months. Aureomycin, Terramycin, and streptomycin are also effective, but penicillin seems to be the

drug of choice for congenital syphilis. Failures require a second course of penicillin plus arsenicals.

TYPHOID FEVER

In typhoid fever[106, 107] and in typhoid carriers Chloromycetin is the drug generally found most effective; 50 mg. per kilogram given as the first dose, followed by 250 mg. every three to four hours for seven to ten days after the temperature becomes normal. Relapses occur quite frequently but many of them respond to additional Chloromycetin. While Chloromycetin treatment of typhoid fever may reduce the incidence of carriers, it is now becoming more evident that carriers may not clear up under antibiotic therapy alone.

BACTERIAL PNEUMONIA

In the bacterial pneumonias penicillin and sulfadiazine are the drugs of choice. The broad spectrum antibiotics are also quite effective in pneumococcus pneumonias. Although one or two days of treatment usually suffice in most pneumonias, treatment should be continued for two to three days after the temperature becomes normal. Pneumonia in infants under one year of age is frequently due to a staphylococcus. Penicillin plus Aureomycin or Terramycin yield best results.

VIRUS OR PRIMARY ATYPICAL PNEUMONIA

Many authors have reported prompt improvement following the use of Aureomycin, Terramycin, or Chloromycetin, in many instances after previous penicillin therapy seemed to have been unsuccessful. In viral infections of the lung it is often very difficult to separate the viral from the bacterial role in the disease. It may be equally difficult to determine whether the beneficial results derived from the broad spectrum antibiotics was due to antibacterial or antiviral action. Since antiviral activity of these antibacterial drugs seems to be limited to the larger virus, psittacosis, lymphogranuloma venereum, etc., the effect noted was probably antibacterial. Nevertheless, it has been suggested that if along with the pneumonia there is a rise in cold agglutinins, and if penicillin seems to be ineffective, the introduction of Aureomycin or Terramycin may be warranted.[108] If not effective in two to three days it is probable that further antibiotic therapy would be of no avail.

COMMON COLDS

Neither the antibiotics nor sulfonamides are effective in the common cold. This is in keeping with the lack of effect with these drugs in common virus diseases. Indeed it is a common experience in hospital wards for children who are receiving penicillin, Aureomycin, Chloromycetin, Terramycin, sulfadiazine, each alone or in combination, to develop all the signs and symptoms of the common cold or grippe, and even influenza. Nevertheless, since secondary bacterial invaders rapidly complicate the common cold producing otitis media, cervical adenitis, sinusitis, or pneumonia, one may introduce these drugs with beneficial results in the more severely affected. Antibiotic therapy is especially indicated for children who have frequent upper respiratory infections and who harbor pathogenic bacteria in the nasopharynx.

OTITIS MEDIA, MASTOIDITIS AND CERVICAL ADENITIS

In catarrhal otitis media treatment must be continued for three to four

days after all evidence of ear infection has disappeared. In cases of purulent otitis media treatment must be continued not only until the eardrum is healed but for seven to ten days longer. Should there be a recurrence of otitis media within a week the treatment should be more energetic and another antibiotic, possibly Aureomycin, might be added. If mastoid tenderness or other evidence of mastoid involvement develops and if antibiotic therapy is favored over surgery, it may be necessary to continue treatment for as long as four to six weeks to obtain complete healing, indicated by roentgen findings, a normal blood count, and normal sedimentation rate.

In the management of cervical adenitis, energetic treatment is indicated not only for the duration of the fever, swelling, and tenderness of the gland, but for several days thereafter.

Penicillin is the drug of choice in cervical adenitis, otitis media, and mastoiditis. In resistant staphylococcus infection Aureomycin added to the penicillin produces more rapid results. If the Friedländer's bacillus is the infecting agent streptomycin is the choice. Local treatment with ear drops of Aureomycin, Terramycin, bacitracin, polymyxin, or neomycin may be helpful in purulent otitis media but is not likely to be as effective as systemic therapy.

SINUSITIS

Acute sinusitis requires the same intensive antibiotic and sulfonamide therapy as do otitis media and cervical adenitis. In addition, penicillin in the form of nose drops or aerosols might be added along with steam inhalations. Pathogens should be eradicated from the nasopharynx and sinuses before therapy is discontinued.

ACUTE NONDIPHTHERITIC LARYNGITIS AND/OR TRACHEOBRONCHITIS

Simple croup may be caused by viruses or bacteria but secondary bacterial involvement is almost the rule. Since it is often difficult at the beginning of the illness to exclude the possibility of the more serious tracheobronchitis, and to anticipate the degree of glottic, subglottic, or supraglottic edema that is present or may quickly develop, it is considered safer to treat each episode with antibiotics which will protect against most of the usual bacteria found, e.g., hemolytic and nonhemolytic streptococcus, *Staph. aureus,* and *H. influenzae.* Liberal doses of intramuscular penicillin and streptomycin or Aureomycin are given. If the oral route is available the Aureomycin may be preferred to streptomycin. It is rarely necessary to continue the Aureomycin or streptomycin for more than three to four days, but the penicillin may have to be continued for longer.

The antibiotics may not correct the condition rapidly enough to relieve the swelling. Tracheotomy when indicated may be lifesaving.

MENINGITIS

Pneumococcus Meningitis.—The simultaneous administration of sulfadiazine and penicillin in liberal doses intravenously, orally, or by both routes is the treatment of choice. If the disease is very severe or is not progressing well with oral and intravenous therapy alone there is little if any risk in one or two intraspinal injections of 10,000 units diluted in 10 c.c. of physiologic saline solution. Treatment may be stopped five to seven days after the temperature has become normal, the

spinal fluid clear of bacteria, and after the spinal fluid sugar has risen to 50 mg. per cent or more.

Aureomycin, Terramycin, and Chloromycetin are also effective against pneumococcal infection and may be given along with penicillin if progress is poor.

For infants and children, penicillin, 1 to 2 million units daily, four times 300,000 units or four times 500,000 units, of aqueous procaine penicillin suffice to cure most cases. This amount of penicillin usually results in spinal fluid levels adequate to eradicate the pneumococcus. I have not had to use larger doses. Nevertheless it is recognized that spinal fluid levels may be quite low on the dosage mentioned. Larger doses of penicillin may be necessary to attain higher concentration and to reach loculations of exudate. Doses of 6, 8, or 12 million units of aqueous procaine penicillin administered intramuscularly in divided doses every two hours have been advised.[109]

Sulfadiazine is given in dosage of 0.2 Gm. per kilogram per day by mouth, or 0.15 Gm. per kilogram per day parenterally until the oral route becomes available. It is continued orally for one week after the spinal fluid becomes normal.

Therapy is started with an intravenous infusion of 500,000 units of penicillin plus the initial dose of sodium sulfadiazine in 250 to 500 ml. of physiologic saline solution.[110] The fluid is permitted to flow in rapidly. For infants and young children give 100 to 250 c.c. in the first hour, then 30 to 60 c.c. per hour; larger amounts are used in older children and adults. After the first day the penicillin is given intramuscularly but the sulfadiazine by vein or subcutaneously unless it can be taken orally.

Streptococcus Meningitis.—Penicillin and sulfadiazine, preferably together, are still the drugs of choice and should be given intravenously and by mouth in liberal doses until seven to ten days after the temperature becomes normal and the spinal fluid is free from bacteria and is otherwise normal. The dosage and procedure are the same as for pneumococcus meningitis. Penicillin may have to be continued until all foci of infection, e.g., middle ear, are completely healed.

Meningococcemia and Meningitis.—In meningococcemia alone or in meningococcus meningitis best results are obtained with sulfadiazine.[111] If the patient's condition precludes oral therapy, sodium sulfadiazine, 75 mg. per kilogram, is given intravenously or subcutaneously as the first dose. Thereafter 0.2 Gm. per kilogram per day is given by mouth or 0.15 Gm. parenterally as warranted by the patient's condition. This is continued until three to seven days after the temperature and spinal fluid have become normal. Penicillin is also effective yet penicillin added to sulfadiazine does not seem to yield better results than are achieved by us of sulfadiazine alone. Aureomycin and Terramycin are also effective, but less than sulfadiazine.

In the acute fulminating form of bacteriemia, the Waterhouse-Friederichsen syndrome, large doses of penicillin and sulfadiazine are given early, but the question of survival is often dependent on the treatment of shock with cortisone.[112] Cortisone is preferred since it is much more effective than Eschatin. Since bacterial dissemination may increase during corti-

sone therapy the sulfadiazine and penicillin must be continued throughout the period of cortisone therapy. Moloshok and Hodes have pointed out that the ability of the adrenal to respond to ACTH with an adequate drop in eosinophils may indicate the duration of need for cortisone therapy.

Influenzal Meningitis.—Streptomycin, 25 mg. per pound or 40 to 50 mg. per kilogram of body weight, given in divided intramuscular injections every six hours for five to six days, preferably with sulfadiazine, is usually effective.[113, 114] In more severe cases, 25 mg. of streptomycin given intrathecally daily for one or two days may be helpful. Sulfadiazine, if included, should be given in dosage adequate to attain a blood level of 10 to 12 mg. Usually 0.2 Gm. per kilogram of body weight per day suffices. Aureomycin is also effective against *H. influenzae* and several patients have been treated successfully by Chandler and Hodes,[115] McGovern and associates[116] and others with Aureomycin alone, or Aureomycin with sulfadiazine added. My limited personal experience is in agreement with McKay, Cook, and Davies[117] that Aureomycin alone or with sulfadiazine may not be adequate. A 3-year-old child whom I treated with Aureomycin, 100 mg. per kilogram daily orally, plus intravenous Aureomycin, 200 mg. b.i.d. for the first two days, improved only to have recurrence of symptoms and a positive spinal fluid culture two days after we had considered the patient cured and therapy was discontinued.

Chloromycetin, 100 mg. per kilogram of body weight, given by mouth or stomach tube as the initial dose followed by a maintenance dose of 100 to 200 mg. per kilogram per day given by gavage at six-hour intervals in doses of 25 to 50 mg. per kilogram of body weight for a total of ten days seems to have become the treatment of choice. Prather and Smith[118] have had very good results using Chloromycetin alone, 100 mg. per kilogram per day. Alexander[119] has likewise concluded that Chloromycetin is the preferred drug for influenzal meningitis. She recommends 100 mg. per kilogram per day intravenously, or 200 mg. per kilogram per day by mouth for a period of ten days.

The results with Chloromycetin alone have been excellent. A combination of either Chloromycetin and sulfadiazine or streptomycin and sulfadiazine is preferred by some and it has been suggested that the choice treatment might be a combination of Chloromycetin, 100 mg. per kilogram of body weight per day, plus streptomycin, 40 to 50 mg. per kilogram of body weight, with or without sulfadiazine. If such a combination is used the Chloromycetin should be given parenterally until the patient can take it by mouth. It is continued until the temperature and spinal fluid have become normal and have remained so for a week, or for a total of about ten days. The streptomycin might be given for only four to five days in dosage of 50 mg. per kilogram of body weight per day, 25 mg. per kilogram being injected intramuscularly every twelve hours. If Chloromycetin is used, frequent blood counts are mandatory and the drug immediately discontinued if any evidence of anemia or tendency to aplasia is noted. Bone marrow examination may be necessary.

Meningitis, Etiology Unknown, or Partly Treated Meningitis.—Many patients with partly treated purulent

meningitis are admitted to hospital wards having received one or two injections of penicillin within the previous two or three days at home, in hospital emergency rooms, or in outpatient departments. Some of these patients may have had one or a mixture of sulfonamides alone or along with the penicillin, or possibly one of the other antibiotics for one or two doses. Oral medication may have been stopped because of vomiting ascribed to drug intolerance rather than to meningitis.

It is not difficult to determine that these patients have meningitis when brought to the hospital because of a convulsion, a stiff neck, and/or a positive Kernig and Brudzinski, but the spinal fluid may be sterile and organisms are either not seen at all or may be present in very small numbers and fail to grow out on culture media. The spinal fluid cell count is usually elevated and the sugar is normal or only slightly reduced. The cells may be predominantly lymphocytes, thus resembling the findings of a virus encephalitis. It is therefore difficult, often impossible, to determine the type of meningitis present. A rapid response to penicillin and/or sulfonamides suggest strongly that it is an infection with either meningococcus or pneumococcus or streptococcus, but since an organism like *H. influenzae* or a staphylococcus may be present, Aureomycin, Terramycin, streptomycin, or Chloromycetin should be added to the penicillin therapy.

The practice of giving a "shot" of penicillin to every infected child seen in a dispensary or in an emergency room or at the patient's home is often wrong and should be condemned as a general practice. Yet it must be admitted that in many instances the one or two treatments have retarded the progress of meningitis or pneumonia and have thus aided in preserving the patient's life.

Tuberculous Meningitis.—Recovery of 35 to more than 50 per cent of the patients treated is attained by intensive therapy including streptomycin intramuscularly and intrathecally, and Promizole or a similar drug or para-aminosalicylic acid are employed simultaneously, except when miliary tuberculosis is present.[120] Then the results are not as good.[121, 122] Those with most extensive experience in the management of tuberculous meningitis stress the need for long protracted and uninterrupted therapy, even though the danger of developing deafness is increased thereby.

Streptomycin is given intramuscularly in dosage of 20 to 50 mg. per kilogram of body weight per day. One and one-half to 2 grams divided into two to four injections is the maximum daily dose given to any patient. This is continued for six, nine, or twelve months or longer as needed. The duration of treatment is dependent on the time it takes for the disappearance of all evidence of active infection in the central nervous system, for the temperature to be normal, the cerebrospinal fluid to be normal, and for the electroencephalogram to become normal or to remain unchanged for several tracings. This usually implies intramuscular treatment for at least two months after the cerebrospinal fluid has become normal.

Streptomycin is given intrathecally in dosage of 20 to 50 mg. depending on the size of the patient. For the first eight to ten days two intrathecal injections may be given daily, but one

daily instillation is more commonly employed. These injections are continued for forty to sixty days, then once every two days for as long as it takes the cerebrospinal fluid to become normal, and for two weeks thereafter.

When Promizole or some equivalent drug is given along with streptomycin the results are said to be better than with streptomycin alone. The drug is given by mouth in dosage of 100 mg. per kilogram of body weight per day. One gram of Promizole daily is given for several days. If there is no evidence of toxicity (nausea or vomiting) the dosage is gradually increased from 1 to 3 Gm., then to 100 mg. per kilogram per day, or until blood levels of 1 to 3 mg. per 100 ml. are obtained. This is continued for a year or more.

Para-aminosalicylic acid (PAS) has been found to be more effective than Promizole in reducing the development of resistance of the tubercle bacillus to streptomycin. It is given in dosage of 0.3 to 0.5 mg. per kilogram per day by mouth, divided into four to six doses, and is continued for three to four consecutive days after which it is omitted for one or two days. This cycle is resumed throughout the course of streptomycin therapy. Others recommend uninterrupted therapy begun one week after streptomycin is started and given in divided doses up to six to ten Gm. daily to obtain levels of 10 to 15 mg. per cubic centimeter.

The advantages of intrathecal tuberculin as recommended by Smith for patients progressing poorly on streptomycin therapy require further corroboration.

Neomycin is as toxic as dihydrostreptomycin and possesses no advantage over it except to be used occasionally when the resistance to it has become very high.

The newer isonicotinic acid derivatives have been used in the treatment of tuberculosis and tuberculous meningitis for too short a time to warrant definite conclusions. Nevertheless beneficial results, occasionally spectacular improvement, have been observed in cases of tuberculous meningitis. These drugs brought about rapid improvement in patients who remained unimproved for as long as three months on streptomycin therapy. The development of resistance of the tubercle bacillus to the isonicotinic acid derivatives has caused considerable concern. It is therefore suggested by some that they be given along with dihydrostreptomycin and para-aminosalicylic acid.

Herewith are listed several diseases and their treatment, as well as other diseases unaffected by antibiotic therapy.

Gas gangrene: Massive doses of penicillin should be tried although not of established value.

Gonorrheal infections: Penicillin, 300,000 units intramuscularly, for one or two days, or 150,000 to 300,000 orally twice daily for one or two days.

Rickettsialpox: Aureomycin, or Terramycin, or Chloromycetin.

Rocky Mountain spotted fever: Aureomycin, or Terramycin, or Chloromycetin.

Typhus (epidemic): Aureomycin, Terramycin, Chloromycetin.

Typhus (murine): Aureomycin, Terramycin, Chloromycetin.

Q fever: Aureomycin.

In the above listed, as well as in all other rickettsial diseases, the three broad spectrum antibiotics yield excellent results if continued until the temperature becomes normal. Choice of one of them over another may depend on individual tolerance, drug toxicity and availability of the drug rather than on the slight therapeutic advantage of one over another.

Salmonellosis: Chloromycetin, 30 to 50 mg. per kilogram per day. Streptomycin (orally), 100 mg. per kilogram per day. Terramycin, 25 to 35 mg. per kilogram per day. Sulfadiazine, Sulfasuxidine, and Sulfathaladine.
Tetanus: Large doses of parenteral penicillin may be helpful but these are not antitoxic. Antitoxin should be administered.
Tularemia: Streptomycin is very effective; Aureomycin and Chloromycetin are effective.

Diseases in which antibiotic therapy is of no proved value except for the bacterial complications:

Chicken pox.
Coccidioidomycosis.
Encephalitis, equine eastern.
Encephalitis, equine western.
Encephalitis, St. Louis type.
Exanthum subitum.
Infectious hepatitis, infectious lymphocytosis, infectious mononucleosis.
Histoplasmosis.
*Influenza, viral.
Lymphocytic choreomeningitis.
*Measles and mumps.
2OaH
†Poliomyelitis.
Rabies.
German measles.
*Smallpox.
Toxoplasmosis: sulfadiazine has resulted in suggestive results.
*Virus pneumonia.

LOCAL THERAPY

All of the antibiotics which have limited use because of their toxicity have been found to be quite effective when applied externally. All antibiotics, penicillin, the broad spectrum antibiotics, tyrothricin, gramicidin, bacitracin, aerosporin, and neomycin are now available alone or in combination to cover the gram-negative and gram-positive organism in form of ointment, troches, and in liquid form to be used as nose drops or eye drops. While some like penicillin may produce local sensitization, others like bacitracin are less prone to produce local allergy.

*Antibiotic therapy is indicated because of the frequency of bacterial complications.

†Antibiotic therapy is indicated in the bulbar type and those with tracheotomy because of the frequency of pulmonary complications.

PROPHYLAXIS

The prophylactic use of antibiotics against secondary bacterial complications in viral diseases like measles, influenza, and the common cold have already been discussed. Brief reference will now be made to the choice of antibiotics found useful in prophylaxis of some other common conditions.

Diphtheria.—A Schick-positive individual previously immunized with toxoid or toxin antitoxin when exposed to diphtheria should receive a booster dose of fluid toxoid plus daily injections of 600,000 units of aqueous procaine penicillin for five to seven days. He must be examined daily and antitoxin must be given at the first suggestion of clinical diphtheria.

A Schick-positive individual not previously immunized, when exposed to diphtheria should be treated as above minus the injection of toxoid. In addition, daily nasopharyngeal examination should be made and antitoxin given if a positive culture is obtained or at the earliest appearance of suggestive signs and symptoms of diphtheria. Penicillin should be started promptly after the culture is obtained.

A Schick-positive individual who is sensitive to horse serum and has been exposed to diphtheria is given a booster dose of fluid diphtheria toxoid prophylactically plus penicillin daily and observed for clinical signs or symptoms of the disease. At the first suggestion of diphtheria, horse serum desensitization should be followed by antitoxin therapy. The toxoid might be omitted if he had not been previously immunized.

Scarlet Fever.—It has been my practice to treat prophylactically sibling and adult contacts of scarlet fever with

1 or 2 Gm. of sulfadiazine daily or 300,000 units of aqueous procaine penicillin daily, or 200,000 units of oral penicillin three times daily for seven days. In the contacts so treated no secondary cases of scarlet fever or tonsillitis were noted.[123]

Meningococcal Infections.—Contacts of meningococcus-infected patients such as nurses, family, and dormitory roommates may and often do become carriers, and sometimes develop meningococcemia and meningitis.[124] One to 2 Gm. of sulfadiazine daily rapidly eliminates infection in most of these carriers. Penicillin should be given to those unable to tolerate the sulfonamides.

Rheumatic Fever.—Penicillin[125] and sulfadiazine[126] 0.5 to 1.0 Gm. daily, have been used with some success in individuals convalescent from rheumatic fever, as well as in special wards or institutions for rheumatic children. These drugs largely eliminate the hemolytic streptococcus from the patients and have thus reduced the recurrences of rheumatic fever by about 60 per cent. Some advocate that this form of prophylaxis be continued up to five years, or until the child attains the age of 15 years, after which the recrudescence of rheumatic fever is less likely. Bicillin,[127] 1,200,000 units, given once in two weeks is said to result in adequate blood levels to avoid infection with the hemolytic streptococcus.

In the above paragraph the prophylaxis was for recurrent episodes of rheumatic fever. It is also possible to reduce the incidence of primary episodes of this disease. Initial attacks of rheumatic fever might be prevented by promptly treating all forms of disease caused by group A streptococci. Group A streptococci are eliminated from individuals ill with scarlet fever or sore throat without an exanthem by the use of penicillin, Aureomycin, sulfadiazine, and other antibiotics and sulfonamides. Penicillin is the preferred drug.[78] Seven to ten days of continuous therapy results in the smallest per cent of reappearance of the streptococci and both penicillin or Aureomycin cause a reduction in the incidence of rheumatic fever as compared with untreated controls.

Of a group of 1,650 cases of streptococcal infection in one Army camp, half were treated with penicillin and half served as controls.[78] Only two instances of rheumatic fever were observed in the treated group, while in the untreated group seventeen patients developed rheumatic fever. This is statistically significant and indicates the need for early treatment of hemolytic streptococcal infection.

Tonsillectomy.—Penicillin is also given prior to and for several days after tonsillectomy to reduce infection.

Subacute Bacterial Endocarditis and Congenital Heart Disease.—Penicillin is used routinely prior to and after operation for patent ductus arteriosis, as well as for surgery of other congenital heart lesions. When subacute bacterial endocarditis is associated with the congenital heart disease for which surgery is contemplated, treatment with an appropriate antibiotic until the infection is cured is recommended prior to surgical intervention.

Tooth Extraction.—Penicillin being effective against streptococcus viridans is also used prophylactically prior to and after tooth extraction to avoid infection with streptococcus viridans.[124]

Abdominal Surgery.—Surgeons prefer to treat patients with oral strepto-

mycin, Aureomycin, or Chloromycetin plus penicillin for three to four days before intestinal surgery.[128] For peritonitis following appendicitis penicillin and streptomycin are commonly employed. Aureomycin, Chloromycetin, or Terramycin may be substituted for the streptomycin as soon as the child is permitted oral therapy.

Surgery in Tuberculous Patients.—Dihydrostreptomycin is recommended for a period of ten to fourteen days before and after surgery for active tuberculosis.

Ophthalmia Neonatorum.—Penicillin is gaining popularity as a substitute for silver nitrate in the ocular prophylaxis in the newborn infant.[129, 130] It is more effective than silver nitrate and causes less local complications. Penicillin is administered either as eye drops, as the ophthalmic ointment, or as an intramuscular injection of 50,000 units. The eye drops are probably the least effective of the three.

Cystic Fibrosis of the Pancreas.—In cystic fibrosis of the pancreas the pulmonary infections are of prime importance.[131] Fifty thousand units of penicillin given in aerosol two or three times daily has been helpful and more recently Aureomycin and Terramycin given orally or as aerosol have also been found useful.

Burns.—Antibiotics are helpful in prevention as well as treatment of infection secondary to burns, but they are not invariably successful in avoiding bacterial contamination.

Urinary Infection.—Antibiotics are often given to prevent recurrence of urinary tract infection with varied success. Some bacteria are eliminated only to have others appear which are resistant to the agent used.

The conditions already mentioned are but a few of those in which antibiotics and sulfonamides are used for prophylaxis. Clinical and experimental justification are available for this extensive prophylactic use of the antibiotics. However, in many instances the clinical data are still inadequate to establish the procedure beyond doubt.

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Psychologic Aspects of Pediatrics

POOR APPETITE IN THE NEWBORN AND YOUNG INFANT

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

ALTHOUGH the appetite not infrequently begins to fall off during the last quarter of the first year, poor appetite does not ordinarily become a problem until the second year of life. In rare instances, however, infants appear to be without hunger from the start.

Von Reuss[1] has observed newborn infants who suck poorly. They grasp the nipple weakly or not at all, quickly lose interest in sucking and stop or fall asleep. This condition generally lasts only a few days but it may persist for months. The children, though usually small at birth, appear normal in every other way. They gain weight slowly during the first half year, appearing delicate, but thereafter they go ahead rapidly, making up their deficit in weight and developing into normal children. Von Reuss regards their progress as resembling that of prematurely born infants.

Gesell and Ilg[2] describe infants in whom the intake of milk is small and the appetite weak. They rarely give evidence of hunger by crying and show little or no eagerness for food. Ordinarily the nipple is accepted at the beginning of the feeding but interest wanes quickly; sometimes the nipple is decisively refused even at the beginning. Such children sleep a great deal, seemingly preferring sleeping to eating.

Finkelstein[3] mentions a child in whom the sucking reflex was almost completely absent until the sixth month and whose later physical and mental development was quite normal.

In 1928 Feldstein[4] described an infant girl who refused breast and bottle from the beginning. Though she would take some food while dozing in the dark, the intake was not adequate and she had to be fed by tube. Despite the feeding difficulty, mental and motor development was normal. At one year she weighed 16½ pounds (7.46 kilograms).

In a later report Feldstein[5] described the same girl at 21 years. In appearance she was a normally developed adult, 5 feet 6 inches (165 centimeters) tall, weighing 135 pounds (61.3 kilograms). She had no special personality or behavior problems, though she was short tempered and was subject to violent rages. She had finished a four-year college course making average grades without too much studying. She was clever, witty, popular with both sexes and made and held friends easily. Her appetite was indifferent. On the whole she seemed a normal young woman.

We have also observed an infant who appeared uninterested in food from birth. The patient, a boy, was the younger of two children. He was born at term weighing 5 pounds 5 ounces (2.41 kilograms). The older child, a girl, was 4 years old and was in every respect normal. The parents were normal, the prenatal course and birth without incident.

From the Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center.

The baby was thin and delicate looking at birth. Examination was negative except for a small lower jaw, the baby in this respect resembling his father. The tongue was in the normal position and there was no respiratory difficulty except, at times, during feeding.

From the beginning the baby sucked and swallowed poorly. Spoon feeding was begun during the first week of life. The child continued in this way, getting some food by sucking, some by spoon, and at 10 weeks he weighed 8 pounds 4 ounces (3.75 kilograms), a gain somewhat better than half the expected increase at this age. At all times he showed a complete lack of interest in eating, and feeding him was a continuous chore. He was fed in the upright position; feeding in the prone position was unsuccessful. At no time did he show the discomfort commonly associated with hunger. Nor did he lapse into contented quiescence after he had been fed.

At 10 weeks of age, coincident with a change in nurses, feeding difficulties increased and a loss of weight to 7 pounds 4 ounces (3.3 kilograms) ensued. Aspiration of food was suspected but there was no cough, examination of the chest was negative (except for rhonchi which were interpreted as being transmitted from the larynx), and a film of the chest was negative. From time to time the baby became cyanotic during feeding and had to be aspirated.

Tube feeding was instituted when the baby was 15 weeks old. A prompt increase in weight followed, the baby gaining 12 ounces (360 grams) in the first six days. During the time that he was tube fed, he showed increasing signs of hunger and by 19 weeks he was weaned from the tube and fed by spoon and bottle. His weight at this time was 10 pounds (4.56 kilograms). He continued to progress. At 6 months he was a normally alert baby weighing 12 pounds 9 ounces (5.7 kilograms).

Many theories have been suggested to account for poor sucking, without demonstrable organic cause, in early life. There is no evidence for Birk's[6] view that the cause is minor cerebral injury; nor for Finkelstein's suggestion of "constitutional neuropathy" since these infants, so far as is known, develop normally later on. Cameron[7] proposes the early development of negativism as the etiological mechanism but here, too, evidence is lacking. Ivy[8] suggests, as an explanation for the apparent absence of hunger sensation, "an inadequate development of the pain nerves in the stomach. Consequently the infant shows no hunger distress after not being fed for several hours, and no quieting reaction after being fed. Another possibility is that some factor is operating, not detectable by the physician, which inhibits hunger contractions."

Organic causes to be considered when a newborn infant refuses to suck are prematurity, intracranial lesions including subdural hematoma, deformities or ulcers of the mouth or lips, macroglossia, hypoplasia of the mandible, a nipple which is difficult for the baby to grasp, an inadequate milk supply, faulty nursing technique.

Infants with congenital poor appetite are to be distinguished from the rare instances of breast-shy infants. The characteristic here is an aversion to sucking at the breast to such an extent as to lead to interfer-

ence with weight gain. Whenever the child is put to the breast he cries lustily, turns the head away sharply, pulls at the nipple or shies away from it. It is said that such infants take the rubber nipple readily, and that they will also take the breast if fed in the dark, when blindfolded, or when dozing. In infants with breast shyness the appetite and the mother's breasts are normal. The infants, instead of appearing delicate and frail as in the case of the poor eater, appear strong and vigorous. Treatment of the breast-shy infant is simple, requiring merely bottle feeding.

A certain number of children manifest poor appetite at about 3 months. Interest in the breast or bottle lags, new foods are accepted critically, and later on lumpy foods are accepted with great protest. These children are poor chewers and often insist on being fed by the same person, in the same place, and so on. They generally remain poor feeders during the entire preschool period.

Such a case was J. G., a girl. She was the first and only child. The father was a pediatrician. She was delivered normally at term weighing 7 pounds (3.2 kilograms). She was breast fed. She sucked fairly well, seemed contented and gained well. Breast feeding was discontinued at 10 weeks because the mother acquired an infection. The weight at this time was 12 pounds (5.5 kilograms).

The infant was given a proprietary milk preparation. She seemed satisfied with only 10 to 15 ounces (300 to 450 c.c.) daily. She never took more than 20 ounces (600 c.c.). Solid foods were introduced at 3 months but she showed no interest in them. The parents date the feeding difficulties from this time. At 5 months she would take small amounts of banana and somewhat later 2 to 3 teaspoonfuls of puréed fruits and cereal. At 7 months she weighed 15 pounds, 14 ounces (7.2 kilograms) and was 26 inches (65 centimeters) tall. Feedings were accepted best while the baby was about to fall asleep.

Despite the feeding difficulties the baby appeared alert and happy and slept well. General development proceeded normally.

At one year she weighed 18½ pounds (8.4 kilograms). At about this time her intake of solid food improved decidedly. At 23 months she was taking a fairly varied diet of solid food. In a typical day she would take 6 to 8 tablespoonfuls of precooked cereal, one jar of strained fruit, an egg, 4 to 6 tablespoonfuls of scraped beef and about 10 ounces (300 c.c.) of milk. Her weight at this time was 23 pounds (10.4 kilograms), her height 33 inches (83 centimeters). She was feeding herself fairly satisfactorily and appeared in every way a happy, contented baby. She was still a poor chewer.

DISCUSSION

Poor appetite in children, unassociated with demonstrable organic disease, is generally regarded as psychogenic. Young children find in finickiness about food and in refusal to eat a ready means of asserting themselves, of gaining attention, and of spiting their parents. These reactions on the part of children are elicited and reinforced by parental overdirection and rejection, by parental insistence on particular foods which they have been led to believe are "good" for

their children, and by feeding uninterestingly prepared foods.

It is apparent that there are innate differences in the intensity with which hunger sensation is experienced and that certain children may be poor eaters from birth or early infancy on the basis of their genetic endowment. As the usual circumstances leading to poor appetite in young children are becoming more clearly understood, and as measures are being taken to avoid them, one may expect that an inborn poor appetite will become a more important consideration in assessing the child who eats poorly.

SUMMARY

1. Poor appetite without demonstrable organic basis is occasionally observed in newborn and young infants. So far as is known these individuals develop normally.

2. Apparently there are inborn differences in appetite which must be considered in assessing the factors leading to poor appetite during childhood.

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Comments on Current Literature

ENDEMIC POLIOMYELITIS

THE concept that in the tropics poliomyelitis is an endemic disease, and that infection with the virus of poliomyelitis is widespread in the early years of life in these areas has received support from epidemiologic studies carried out within recent years.[1, 2, 3] A study by Melnick and Ågren reported in the *Proceedings of the Society for Experimental Biology and Medicine*[4] supplements earlier observations and adds further information on this important subject. The investigation was carried out in the neighborhood of Cairo, Egypt, where previous studies[1] had indicated infection of the population with the virus of poliomyelitis. The paralytic attack rate for the disease has been appreciable in infants in this area, but paralytic poliomyelitis is unusual in adults. A serological survey made in 1950 on "normal" serum specimens collected in Egypt indicated that neutralizing and complement fixing antibodies to all three types of poliomyelitis virus are acquired at an early age by native Egyptians.

In an extension of these earlier observations, Melnick and Ågren collected rectal swab specimens from thirty-six apparently normal infants living in this area, and ranging in age from 6 to 12 months. These rectal specimens were prepared as ten pools, and the samples to be tested inoculated intracerebrally into monkeys, subcutaneously into white Swiss mice one day of age, and cultured for the presence of virus in monkey testicular tissue by the roller-tube method. A number of strains of virus were isolated from the pools of these thirty-six rectal specimens: one strain of poliomyelitis virus isolated by monkey inoculation, nine strains of Coxsackie virus isolated by mouse inoculation, one strain of Coxsackie virus by tissue culture, and also by tissue-culture inoculation, a strain of virus which could not be classified as belonging to any of the known types, but which was shown to have cytopathogenic properties for monkey testicular tissue, producing definite degeneration of fibroblasts. The newly isolated strain is not infective for monkeys, mice, or hamsters, and as yet information concerning its nature is not sufficient for identification.

These results reported by Melnick and Ågren are in accord with the findings of Gear and his associates[2, 3] who were able to demonstrate that four of sixteen native infants studied in the area of Johannesburg, South Africa, were excreting virus at some period during the first year of life, and in another instance, that five of nine South African babies tested were excreting Coxsackie virus in their feces. Only one of the twenty-five infants whose stools were tested for virus had shown any signs of illness.

That strains of poliomyelitis and Coxsackie virus have a rather wide natural distribution in Egypt is borne out also by the recent work of Ward.[5] Ward was able to isolate with ease both Coxsackie virus and the virus of poliomyelitis from flies collected in this same region.

From time to time the paralytic rate for poliomyelitis in Egyptian infants has been reported as appreciable, but the disease does not occur apparently with any degree of frequency in native adults in this area. The presumption seems warranted that infection of the population takes place early in life and that immunity is acquired by natural means.

Results obtained in studies such as these have important implications. They re-emphasize the entire problem of acquiring immunity or achieving immunization against infectious agents at an age when there is apparently little damage to the host, in contrast

to the older individual, child or adult, who has not acquired immunity, and in whom an infection with an agent such as that of poliomyelitis may result in central nervous involvement with residual damage. Actually the problem of maintaining immunity in poliomyelitis may not be very different from that in smallpox or diphtheria. It has been shown by recent epidemiologic studies[6] that in communities where smallpox is no longer endemic, a significant percentage of the population will not remain immune to smallpox infection, and that artificial means of producing adequate levels of immunity must be assured by repeated vaccinations with vaccinia virus. Similar findings have been reported concerning loss of immunity to diphtheria[7] due apparently to lack of endemic foci of the disease in a community and the absence of repeated exposure to this disease-producing agent.

While modern improvements in hygiene and sanitation have resulted in a significant reduction in the rates of mortality due to infection with many disease-producing agents, the situation may be quite different with respect to certain diseases, principally virus diseases such as poliomyelitis, since the population's opportunity for natural immunization may be removed, at least in part. Consequently it would be desirable that adequate forms of active immunization be substituted which will compensate, as it were, for one of the disadvantages of civilization.

RUSSELL J. BLATTNER

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THE PREVENTION OF RHEUMATIC FEVER

A SPECIAL committee of the American Heart Association issued a statement in February outlining the prophylaxis of rheumatic fever. While there are different viewpoints as to the way the antibiotics and sulfones should be used, their value and dosage, this statement agreed upon by a group of workers in this field represents as near an authoritative plan as can be reached at the present time. For this reason the JOURNAL publishes that part of the statement which has to do with the treatment and prevention of streptococcal infection.

—The Editor.

I. *Treatment of Streptococcal Infections*

In order to be effective, treatment should be started immediately when a streptococcal infection is suspected and continued for sufficient time to eradicate the streptococci from the throat.

Penicillin is the drug of choice for treating streptococcal infections.

Both the oral and the intramuscular routes of administration have been utilized successfully for penicillin therapy of streptococcal infections. Intramuscular injections have been proved to prevent rheumatic fever. The data on the value of oral penicillin as a preventive is less complete.

Oral administration in contrast to intramuscular administration has these advantages:

(1) It is not as distasteful to many patients.

(2) It requires fewer physician visits.

It has these disadvantages:

(1) Larger amounts of penicillin must be used.

(2) It is difficult to administer to vomiting or refractory children.

(3) In some adults it gives rise to persistent diarrhea and pruritus ani.

(4) It is difficult to be sure that treatment is continued for sufficient time and given in proper relation to meals to be effective.

1. *Recommended Schedules*

a. Intramuscular Penicillin

(1) Children—one intramuscular injection of 300,000 units of procaine penicillin with aluminum monostearate in oil *every third day for three doses.*

(2) Adults—one intramuscular injection of 600,000 units procaine penicillin in aluminum monostearate *every third day for three doses.* (Note: Less preferable, but usually effective—two doses as above at three-day intervals).

b. Oral Penicillin

(1) First five days: 200,000 to 300,000 units one-half to one hour before meals and at bedtime (total of 800,000 to 1.2 million units per day in four divided doses. Smaller amount for children—larger amount for adults).

(2) Second five days: 200,000 to 250,000 units one-half to one hour before meals (total 600,000 to 750,000 units per day in three divided doses).

Note: To be effective, therapy should be continued for the entire ten days even though the temperature may return to normal and the patient may feel better within one or two days.

c. Combination of Intramuscular and Oral Penicillin

Therapy may be begun with one injection of penicillin (300,000 units procaine penicillin with aluminum monostearate in oil) and then, beginning three days after the injection, continued for an additional seven days with oral penicillin according to the schedule b (2) outlined above.

d. Other Medication

(1) Aureomycin is less effective than penicillin in controlling streptococcal infection but is especially useful in those sensitive to penicillin. Dosage: Total 10 mg. per pound of body weight in four divided doses daily for two days. Cut dose in half for remaining eight days of therapy.

(2) New preparations of penicillin. These may be effective and even preferable to the treatment schedules outlined, but at present they have not had sufficient trial to warrant their recommendation.

(3) Other antibiotics: At present there is inadequate data on their value.

e. Not Recommended for Treatment

(1) Penicillin troches or lozenges.

(2) Penicillin followed by sulfonamides.

(3) Sulfonamide drugs.

Note: Recurrences of streptococcal infection should be treated as primary attacks.

II. *Prevention of Streptococcal Infections*

A. *General Rules for Prophylaxis*

1. *Who should be treated?*

All individuals under the age of 18 who have had rheumatic fever or chorea and all those over this age who have had an attack within five years.

2. *When should prophylactic treatment be initiated?*

At the end of the second week of the attack of rheumatic fever or any time therafter when the patient is first seen.* Prior to the start of prophylaxis, beta hemolytic streptococci should be eradicated by proper treatment of the patient.

(See methods of penicillin therapy recommended above.)

3. *How long should prophylaxis be continued?*

In children, at least to the age of 18; in all those above this age, for at least five years from their last attack.

4. *Should prophylaxis be continued during the summer?*

Yes.

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*In patients receiving ACTH or cortisone, be cautious that other infections are not masked since the prophylactic dose is inadequate to treat such concurrent illnesses as pneumonia or meningitis.

B. *Prophylactic Methods*

1. *Sulfadiazine*

This drug has the advantage of being easy to administer, inexpensive and effective (other newer sulfonamides are probably equally effective). Although resistant streptococci have appeared during mass prophylaxis in the Armed Forces, this is rare in civilian populations.

a. *Dosage*—from 0.5 to 1.0 Gm. taken each morning throughout the year. The smaller dose is to be used in children under sixty pounds.

b. *Toxic Reactions*—these are infrequent and are usually minor. However, in any patient being given prophylaxis with sulfonamides consider all rashes and sore throats as possible toxic reactions to the drug, especially if they occur in the first eight weeks of prophylaxis. The chief toxic reactions are:

(1) Skin eruptions

(a) Morbilliform—much like measles—continue drug with caution.

(b) Urticarial—best discontinue treatment.

(c) Scarlatiniform—often associated with sore throat and fever. Unsafe to continue drug.

(2) Blood reactions

(a) Leukopenia—Discontinue if white blood count falls below 4,000 and polynuclear neutrophils below 35 per cent because of possible agranulocytosis which is often associated with sore throat and a rash. Because of these reactions, weekly white blood counts are advisable for the first two months of prophylaxis. (The use of sulfonamides therapeutically for any reason in this period should be preceded by a white blood count.) The occurrence of agranulocytosis after eight weeks of continuous prophylaxis with sulfonamides is extremely rare.

2. *Penicillin*

Although experience with oral penicillin for the prophylaxis of rheumatic fever is more limited than that with the sulfonamides, the antibiotic promises to be a safe and effective prophylactic agent. Oral penicillin has the desirable characteristics of being bactericidal for hemolytic streptococci and of rarely producing serious toxic reactions. It has the disadvantages of being more costly than sulfadiazine and, because of the need of giving it on an empty stomach, of being somewhat more difficult to administer.

Oral penicillin represents an alternative drug for rheumatic fever prophylaxis. It is especially important to use this agent for those who do not tolerate sulfadiazine.

a. *Dosage*—Although other routines of administration may prove satisfactory, the following schedules are suggested:

200,000 to 250,000 units two times daily is recommended. Since penicillin is best absorbed on an empty stomach, the time of administration should be one-half to one hour before a meal or at bedtime. A single dose of 200,000 to 250,000 units before breakfast is less preferable.

b. *Toxic Reactions*

(1) Urticaria

(2) Reactions similar to serum sickness—they include fever and joint pains and may be mistaken for rheumatic fever.

(3) Angioneurotic edema

Although many individuals who have had reactions to penicillin can subsequently take the drug without trouble, it is safer not to use penicillin, if the reaction has been severe and particularly if angioneurotic edema has occurred.

BURTIS B. BREESE, M.D., Chairman,
Committee on Prevention of Rheumatic Fever
MARJORIE T. BELLOWS
EDWARD E. FISCHEL, M.D.
ANN KUTTNER, M.D.
BENEDICT F. MASSELL, M.D.
CHARLES H. RAMMELKAMP, JR., M.D.
EDWARD R. SCHLESINGER, M.D.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Baltimore, Md., Feb. 20, 21, and 22, 1953.

Dr. Lester M. Abelman, 201 Lexington St., Belmont 79, Mass.

Dr. Leonard Apt, Children's Medical Center, 300 Longwood Ave., Boston 15, Mass.

Dr. Gayle Gardner Arnold, 414 W. Franklin St., Richmond 20, Va.

Dr. Dwight Ransford Ashbey, Jr., 237 E. Orange St., Lancaster, Pa.

Dr. Sugrahmanya Balakrishnan, Room 449, Central Y.M.C.A., 40 College St., Toronto, Ontario, Canada.

Dr. Lee Well Bass, Children's Hospital, Pittsburgh, Pa.

Dr. William Allen Bauman, 101 Cooper Dr., New Rochelle, N. Y.

Dr. Edward P. Benbow, Jr., 371 N. Elm St., Greensboro, N. C.

Dr. Norman H. Blatt, 3026 S. California Ave., Chicago 8, Ill.

Dr. Ethel Mina Bookhalter, 451 E. 14th St. (Apt. 10 G), New York, N. Y.

Dr. Geo. W. Brown, 305 W. Rusk, Tyler, Texas.

Dr. Robert John Burke, 16 Hampton Village Plaza, St. Louis, Mo.

Dr. Arnold John Capute, U. S. Army Hospital, Ft. Hamilton, Brooklyn, N. Y.

Dr. Hugo M. Cardullo, 1275 A.S.U., U. S. Army Hospital, Ft. Hamilton, Brooklyn, N. Y.

Dr. Daniel D. Casden, 984 Fenwood Dr., Valley Stream, N. Y.

Dr. John Edward Cassidy, 8905 Oneida Lane, Bethesda 14, Md.

Dr. Gordon Cherwitz, 375 Morris Ave., Providence, R. I.

Dr. Hilary H. Connor, 264 Reservoir Ave., Providence, R. I.

Dr. Robert P. Crawford, 1277 ASU, USAH, Camp Kilmer, N. J.

Dr. Lewis Robbins Day, 4120 Federal Blvd., Denver 11, Colo.

Dr. Antoni Mills Diehl, U. S. Naval Hospital, Great Lakes, Ill.

Dr. John A. Duggan, 133 Pearl St., Cambridge, Mass.

Dr. R. Donald Eney, 709 Anneslie Rd., Baltimore 12, Md.

Dr. Kalman Faber, 255 South 17th St., Philadelphia, Pa.

Dr. Miguel A. Firpi, P. O. Box 9775, Santurce, Puerto Rico.

Dr. Mortimer James Folston, 3016 Nichols Ave., S. E., Washington, D. C.

Dr. Willard E. Forney, 2819-B Baywater, San Pedro, Calif.

Dr. Franklin D. Freda, 63 N. 4th St., Newark, N. J.

Dr. Harry J. Fryer, General Delivery, Charlestown, Md.

Dr. Albin Gedarovich, U. S. Naval Hospital, St. Albans, L. I., N. Y.

Dr. Herbert D. Glick, 8301 Piney Branch Rd., Silver Spring, Md.

Dr. Marvin Green, 4707 Bell Blvd., Bayside, N. Y.

Dr. Donald Gribetz, Children's Med. Serv., Massachusetts General Hospital, Boston 14, Mass.

Dr. Carl Newton Haggard, 1729 Sunset Blvd., Houston, Texas.

Dr. Francis J. Harrington, 12 Darby Rd., Milton, Mass.

Dr. Lloyd Norman Hazen, 160 Washington St., Weymouth 88, Mass.

Dr. Marianne Hessel, 1501 S. Catalina Ave., Redondo Beach, Calif.

Dr. Frank Hamilton Horton, U. S. Naval Hospital, Great Lakes, Ill.

Dr. Patricia H. Husson, 5620 Woodmont Ave., Baltimore 12, Md.

Dr. Robert A. Irvin, 134 S. St. Clair St., Painesville, Ohio.

Dr. Robert I. Jaslow, 598 Lincoln Way East, Chambersburg, Pa.

Dr. Joseph Clay Jenkins, 394 Walworth Dr., Euclid 23, Ohio.

Dr. Ian Bruce Johnston, 1590 Cherry Lane, Lafayette, Calif.

Dr. Solomon A. Kaplan, 2316 Victory Parkway, Cincinnati, Ohio.

Dr. Richard Dudley Kershner, U. S. Naval Hospital, Camp Lejeune, N. C.

Dr. Harry King, 8 Grammercy Park, New York 3, N. Y.

Dr. William B. Knaus, Murphy Building, Suite 635, East St. Louis, Ill.

Dr. Joseph W. Kresock, 77 Maple St., Springfield, Mass.

Dr. Leonard I. Lesser, 1521 University Ave., Tuscaloosa, Ala.

Dr. Morrison S. Levbarg, 310 West End Ave., New York, N. Y.

Dr. Frank W. McCarthy, Jr., 576 Farmington Ave., Hartford, Conn.

Dr. Dan Goodrich McNamara, Cardiac Clinic, Harriet Lane Home, Johns Hopkins Hosp., Baltimore, Md.

Dr. Dolores I. Mendez, 1471 Ashford Ave., Santurce, Puerto Rico.

Dr. Jacob Mervis, 801 Sinclair Bldg., Steubenville, Ohio.

Dr. J. Ellery Michaud, 181 Purchase St., Fall River, Mass.

Dr. Robert Treadwell Miller, 2913 S. 16th Rd., Arlington, Va.

Dr. James William Murphy, 1st Lt., USAF MC, Hdqs., 4430th Med. Gp., 4430th Air Base Wing, USAF Hosp., Langley AFB, Va.

Dr. William Francis Murphy, Jr., 1120 Jamestown Crescent, Norfolk, Va.

Dr. Helen Elizabeth Nash, 1048a N. Vandeventer, St. Louis 13, Mo.

Dr. Robert F. Newton, Brooke Army Hospital, San Antonio, Texas.

Dr. Robert J. Nottingham, 414 High St., Morgantown, W. Va.

Dr. Walter Joseph O'Connor, State Univ. of N. Y. Col. of Med., Dept. of Ped., Kings County Hosp., Brooklyn, N. Y.

Dr. Robert J. Orme, 738 Washington St., Norwood, Mass.

Dr. Joseph Oshman, 201 Medical Dental Building, Corpus Cristi, Texas.

Dr. Richmond Shepard Paine, Children's Hospital, 300 Longwood Ave., Boston 15, Mass.

Dr. Jack Leon Paradise, 4211 Noble St., Bellaire, Ohio.

Dr. Peter J. Pasquariello, 351 Totowa Ave., Paterson, N. J.

Dr. Paul Hammond Pearson, The Johns Hopkins Hospital, Baltimore 5, Md.

Dr. Stuart A. Pomeroy, 815 Ackerman Ave., Syracuse 10, N. Y.

Dr. Howard John Potter, 1444 Massachusetts Ave., Lexington, Mass.

Dr. Mary Robinson Richards, 210 Cedar Lane, Apt. 6-A, Teaneck, N. J.

Dr. Leonard F. Rosenzweig, 155 W. Merrick Rd., Freeport, N. Y.

Dr. Julius Rutzky, 2014 Calvert, Detroit 6, Mich.

Dr. Franklin H. Schaefer, 541 Third Ave., Gallipolis, Ohio.

Dr. Gilbert C. Schreiner, 1st Lt. USAF (MC), U. S. A. F. Hospital, Bryan AFB, Bryan, Texas.

Dr. John Lewis Siddoway, Jr., 4678 Holladay Blvd., Salt Lake City, Utah.

Dr. Maurice Elwyn Snyder, 81 Willard St., Ayer, Mass.

Dr. Lula Belle Therese Stewart, 919 Eastview St., Jackson 36, Miss.

Dr. Michael James Sweeney, 41 Oak Court, Snyder, N. Y.

Dr. Megan Tanner, 1630 N. Vermilion, Danville, Ill.

Dr. Ellsworth Arnold Twible, 58 Fairlawn Ave., N. Weymouth, Mass.

Dr. Robert John Waldron, Lt. (jg) MC, USNR, Armed Forces Staff College, Norfolk 11, Va.

Dr. Maggie Laura Walker, 7415 S. Calumet, Chicago 19, Ill.

Dr. Stuart H. Walker, Fort Meade Army Hospital, Fort Meade, Md.

Dr. Forrest P. White, 1400 Colonial Ave., Norfolk 7, Va.

Dr. Ruth Whittemore, 789 Howard Ave., New Haven, Conn.

Dr. William Kay Woodard, Naval Ammunition Depot, Lualualei, Oahu, T. H.

Dr. Clinton Hannix Wooding, Jr., 1631 Lovitt Ave., Norfolk, Va.

Dr. Ben M. Zweifler, 2907 Kings Highway, Brooklyn 29, N. Y.

The next oral examination will be held by the Board in Philadelphia, Pa., May 1, 2, and 3, 1953.

Dr. Samuel W. Clausen died at the Strong Memorial Hospital in Rochester, N. Y., Dec. 29, 1952, aged 64 years. After his graduation from Johns Hopkins in 1915 he became instructor and associate in pediatrics at the Washington University School of Medicine in St. Louis where he was associated with McKim Marriott in chemical studies in the field of infancy and childhood. In 1924 he was appointed professor of pediatrics at the University of Rochester. He was a member of the American Pediatric Society, Academy of Pediatrics, American Chemical Society, and the Society for Experimental Biology and Medicine.

Dr. Robert H. Alway, assistant professor of pediatrics at the Stamford University School of Medicine, has been appointed professor of pediatrics at the University of Colorado at Denver.

A Fellowship for the study of pediatric allergy, available July 1, is open. Applicants must have completed the intern and resident requirements of the American Board of Pediatrics. Details may be obtained from Dr. Jerome Glaser, 300 S. Goodman St., Rochester 7, N. Y.

A refresher course in pediatrics will be conducted at **St. Christopher's Hospital for Children,** Philadelphia, by the pediatric department of Temple University School of Medicine on June 10 to 13. Each half-day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pa.

On February 25 two announcements were made in regard to gamma globulin. The Red Cross announced that it was turning over 1,714,996 c.c. to the Office of Defense Mobilization, and was processing and packaging 2,000,000 c.c. that had been received through the Department of Defense from the Navy. The combined amount would give approximately 550,000 immunizing doses.

The National Foundation for Infantile Paralysis announced that it was buying the gamma globulin produced by five commercial firms through June 30, 1954. This, processed chiefly from placentas, is effective in infectious hepatitis and measles and will be used for this purpose to conserve Red Cross gamma globulin derived from pooled blood for polio prophylaxis.

At the time of the announcement the Office of Defense Mobilization planned to allocate the gamma globulin to the state health departments. "All allocations of gamma globulin will be made solely by the O.D.M. and all final distribution of the product will be the responsibility of the state health officers" according to the Red Cross announcement.

The Trustees of the Robert Driscoll, Julia Driscoll, and Robert Driscoll, Jr. Foundation of Corpus Christi, Texas, announced the formal opening of the Driscoll Foundation Children's Hospital on Feb. 22, 1953. This 110 bed hospital is the nucleus of the Foundation's efforts to establish the highest quality of medical and surgical service without cost for needy children in Southwestern Texas. Participating in the dedication ceremony were Dr. Arild Hansen of Galveston, Texas, and Dr. Fred H. Howard, medical director of the new hospital.

Book Reviews

Pediatrics in General Practice. James G. Hughes, M.D., New York, 1952, McGraw-Hill Book Co., Inc., 735 pages. Price, $14.00.

So far as the reviewer knows, this is the only pediatric textbook that has been written specifically for the general practitioner. The idea grew out of the author's experience in a midwestern state of giving numerous talks before county medical societies over a period of two years. The book reflects this experience in that emphasis has been placed upon those pediatric problems most frequently encountered by the general practitioner.

There are twelve sections, well illustrated, with numerous charts and tables, and the text material is superbly done. While the writing style is free and easy, as though the author were talking directly to his audience, nevertheless there has been no sacrifice of accurate up-to-the-minute information.

The section on electrolyte and fluid balance is as clear an exposition of the intricacies of this somewhat elusive subject as one can hope to find.

Special comment should also be made about the section on psychological problems of child care. The author has devoted some thirty-five pages to this subject, an indication of the importance he obviously feels should be assigned to this phase of pediatrics. Twenty illustrative cases serve to

point up his general discussion on child psychology.

Throughout the book, the author has taken great pains to be clear, concise, and thorough. Treatment is especially emphasized as it should be in a book intended for the practitioner. Although the title indicates this to be a pediatric textbook for general practitioners, the reviewer is of the opinion that pediatricians will find it equally helpful.

L. F. H.

Tumors of the Central Nervous System (Fascicles 35 and 37 of the Atlas of Tumor Pathology). James W. Kernohan, M.D., and George P. Sayre, M.D., Washington, D. C., 1952, Armed Forces Institute of Pathology, 129 pages, 126 illustrations. Price 90 cents.

Tumors of the Adrenal (Fascicle 29 of the Atlas of Tumor Pathology). Howard T. Karsner, M.D., Washington, D. C., 1950, Armed Forces Institute of Pathology, 60 pages, 47 illustrations. Price $1.00.

Teratomas (Fascicle 9 of the Atlas of Tumor Pathology). Rupert A. Willis, D.Sc., M.D., F.R.C.P., Washington, D. C., 1951, Armed Forces Institute of Pathology, 58 pages, 45 illustrations. Price 50 cents.

These fascicles of the *Atlas of Tumor Pathology*, published by the Armed Forces Institute of Pathology, represent only a small part of the entire *Atlas*. Designed primarily for pathologists, they consist of relatively brief texts profusely illustrated with superb photographs and photomicrographs.

Fascicles 35 and 37, *Tumors of the Central Nervous System*, include an excellent text dealing with tumors of the brain, spinal cord, and meninges, while tumors of the pineal body and other tumors of mesenchymal tissue and of developmental defects are dealt with more briefly. The simplified classification of gliomas and of ependymomas would seem to be a distinct advance over the more cumbersome classifications so frequently employed in the past. The fact that special histologic techniques are not essential for the interpretation of most tumors of the central nervous system should in part dispel the sense of frustration so commonly felt by the pathologist dealing with these tumors.

Fascicle 29, *Tumors of the Adrenal*, includes a number of statements in the text which might be open to controversy. For example, it is stated that sympathicogoniomas almost always occur in or near the adrenal, yet actually these may arise from a variety of sites. The histologic differentiation of sympathicogonioma and sympathicoblastoma is not that commonly employed, and the statement that "metastasis (of sympathicoblastoma) is not frequent or widespread" can hardly be accepted. Of distinct value, however, are the statements concerning the importance of chromation of tissue for the differentiation of cortical tumors and pheochromocytomas, and the emphasis placed upon the lack of correlation between cellular morphology and malignancy both in adrenal cortical tumors and in tumors of the adrenal medulla.

In Fascicle 9, *Teratomas*, the author dispenses with "artificial" subdivisions of teratomas based upon the number of germ layers or upon the solid or cystic nature of the tumor. So-called dermoid cysts of the ovary are therefore included in the general discussion of teratomas. Although superficially this may afford some grounds for confusion (e.g., "Teratomas arise, in order of frequency, in ovaries, testis, etc."), such a simplified classification appears to be valid and should ultimately diminish the confusion so commonly associated with these complex tumors. The author furthermore emphasizes the neoplastic and "nonfetiform" character of teratomas.

These fascicles, while reviewing briefly within their texts the designated subjects, are of greatest importance because of the number and quality of the illustrations. They should be an asset to all who are interested in pathology, but their value to those interested primarily in clinical pediatrics would be limited.

AREY.

Editor's Column

BACTERIAL ALLERGY

THERE is considerable misunderstanding relative to the term "bacterial allergy." From a clinical standpoint symptoms of allergy, as rhinitis and asthma, frequently appear in association with infectious processes, and the results of therapy seem to uphold the concept of cause and effect. "Bacterial allergy" may occur when the infectious process is at the site of the allergic symptoms, as asthma in association with a respiratory infection, or when the two are widely separated, as the association of an ear or skin infection with a nephritis. Some allergists as Dienes, Ratner, and Rackemann maintain that hypersensitiveness frequently follows an infection, and suggest that infection of an acute or chronic nature alters the organs whilch produce antibodies.

One of the chief difficulties in establishing a definite relationship between a bacterial infection and symptoms of an allergic nature lies in the failure of bacterial extracts or vaccines to produce the characteristic immediate whealing type of skin reactions which are so useful in the diagnosis of allergic conditions as hay fever or asthma due to pollens, heterologous serums, foods, etc. It is rare to find such reactions when bacterial allergy is suspected.

Thirty years ago, Zinsser[2] stated, "It has been quite apparent to all workers in bacterial anaphylaxis that sensitization of animals to cell materials of bacteria is much more difficult than is analogous sensitization by serums, egg, and albumin. It has usually been assumed, and we believe correctly, that this was due to the relatively small amount of coagulable protein in the bacterial cell." Dubos[3] stressed the complex antigenic composition of bacteria and the frequency and variety of exposure to bacteria and their products both in health and disease.

Zinsser and his co-workers[4] stated that the fundamental biological significance of bacterial allergy is on an increased specific adjustment of the tissue for response to the stimulus of infection and a consequently enhanced capacity for the rapid mobilization of the protective mechanism. When this mechanism is called into play against a qualitatively and quantitatively slight invasive assault, infection or superinfection may be slowed down or prevented. Peshkin[5] added that this same increased capacity may become injurious or even fatal if called into play in response to an excessive invasive assault.

The problem of bacterial allergy is not simple. It involves allergic sensitization to bacterial products, i.e., the nucleo-protein and/or an endotoxin of the organism concerned. Zinsser[6] said that in bacterial allergy we are dealing with the sensitization of the body by autolytically liberated antigenic substances which are absorbed from any focus in which bacteria react with inflammatory signs and as a result of which the body is rendered sensitive to

contact with these same autolytic products whether they are liberated and absorbed from a chronically existent focus or from a similar focus subsequently acquired. Harley[7] states it clearly when he says, it does not follow that because a streptococcal focus in the tonsils is removed the supply of nucleoprotein allergen to the site of the allergic reaction is completely cut off. Other types of streptococci with similar nucleoprotein may be present in other parts of the body, for example, in the nasopharynx, and continued exposure to this protein substance may be able to keep the reaction going.

In many cases stimulation of the immune mechanism results and adequate amounts of antibody are mobilized so that as an end result immunity develops. Schick[8] proposed the term "physiological allergy" for this type, in that this represents the almost perfect and the most useful defense mechanism of nature against invading pathogenic organisms. However, in some individuals, and this is first seen most clearly in the very young child during the second or third year of life, a history of repeated respiratory infections is common. It is with reference to this group that from a clinical standpoint the term "bacterial allergy" is used. Schick applied the term "pathologic allergy" to this group which is produced by introduction of foreign protein. The reaction is hyperergic. Flensborg[9] stresses the large number of asthmatic children who, during the first four years of life, do not give positive skin tests. He is of the opinion that these children whose asthma starts with respiratory infection suffer from so-called infectious allergy.

There are good reasons for the theory that bacteria themselves or their products may cause an allergic response which can reveal itself in clinical allergy. Cooke listed them as follows: (1) The familial background of allergy is particularly prominent in the acute infectious asthma of infancy and early childhood. (2) The significant association of asthma due to infection with asthma due to inhalants, drugs, or foods, and with other accepted allergies such as hay fever and eczema. (3) Eosinophilia which is present more frequently and to a greater degree in asthma where infection is the sole etiological factor than in those cases of asthma due to inhalants or food allergies, and (4) the most convincing evidence of the allergic nature of asthma due to infection is the fact that the asthmatic attack can sometimes be reproduced either intentionally or otherwise by incredibly small doses of a vaccine.

An understanding of this last statement is important. Anyone who has treated a large number of patients, whether children or adults, whether treated with autogenous or stock vaccine, has observed both immediate and delayed types of allergic response which do not always echo the patient's clinical allergic syndromes. Local reactions which often serve as safety guides are not necessarily present at the site of injection and at times very rapid (within several minutes) or delayed types of anaphylactic reaction (sometimes up to twenty-four hours) occur without any swelling being noted at the injection site.

It is important to remember that bacterial allergy may appear as one of the earliest manifestations of allergy and that in this fertile soil many

other allergies may and do subsequently appear. Frequently, bacterial allergy which has expressed itself in rhinitis is merely the forerunner of the more serious condition of asthma and if proper recognition is paid to the earlier state, it is possible, in many instances, by appropriate and adequate management to prevent asthma.

In the final analysis, the only basis on which the diagnosis of the possibility of specific bacterial sensitization in a patient can be made is the information obtained from a carefully detailed history and repeated clinical observations of the cause and effect of infections on the allergic state. Only then, after a case has been adequately investigated and all other causal factors eliminated, and only from the clinical viewpoint can one arrive at a diagnosis of bacterial allergy.

H. G. RAPAPORT.

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THE MENTALLY RETARDED CHILD

SHORTLY after the discussion by members of the Editorial Board on the question of early institutionalization for the mentally defective child which appeared in last month's JOURNAL was in proof, the Editor's attention was called to a discussion by Drs. Stanley Wolf and Reginald S. Lourie in the January issue of the *Clinical Proceedings of the Children's Hospital of Washington, D. C.* As this presents the viewpoint of the child psychiatrist, permission was obtained to reprint the case report and discussion.

THE IMPACT OF THE MENTALLY DEFECTIVE CHILD ON THE FAMILY UNIT

Case Report No. 254

Stanley Wolf, M.D., and Reginald S. Lourie, M.D.

The care of the mentally defective child is a very difficult problem for even the most well-adjusted parents. The pediatrician is frequently called upon to confirm the diagnosis and to advise the parents concerning the handling of the patient at home or in an institution. If the advice given is not carefully presented, unnecessary anxiety and resentment ensue.

What problems must the pediatrician solve when dealing with a mentally defective child? The physician must ask himself and, ultimately, the family whether or not this child can be kept at home from a financial and emotional standpoint. What will be the effect on the normal siblings, on the parents, on their relatives, and friends? Is their desire for a child so great that they would want even the most seriously retarded infant at home? What is the type and degree of retardation, and what is its prognosis. All of these questions must be carefully considered.

Institutionalization is usually considered at some time in most of these cases regardless of the type of retardation. Too often a physician will recommend this step and then feel discharged of responsibility. The bewildered parent has received no specific information as to available facilities, methods of referral, and cost. In many cases, institutions are not willing to accept a child until he is old enough for group play. It is the physician's responsibility to know the laws peculiar to his area. It is important for him also to recognize the fact that many defective children, especially Mongoloids, have very docile, friendly, affectionate dispositions. If these children are kept in the household, very close emotional ties will be formed between them and their parents. Therefore, institutionalization naturally becomes much more difficult after this period.

The parent of a defective child needs help. He needs conscientious advice, sincerely administered. He needs to know that the physician is available and may be consulted from time to time as problems arise. All too often these parents shop from one medical authority to another in search of help. Frank and understanding discussion on the part of the family pediatrician can frequently prevent this. Many of the points mentioned are illustrated in the following case report.

CASE REPORT

D. H., a 4-year-old white male, was first seen in the medical clinic with the chief complaint of frequent choking spells occurring with upper respiratory infections. The mother also complained that the patient had a speech difficulty. On physical examination the child was noted to have typical Mongoloid facies. No other abnormalities were noted and the patient was referred to the Department of Psychiatry for further study.

In the initial psychiatric interview it was apparent that Mrs. H. was extremely anxious and confused about her son's condition and future status. She had been told that her child was a Mongoloid and was mentally retarded. She did not want the child placed in an institution if this could be avoided. The mother had been referred to this hospital by a private physician to obtain special speech training. With this training, she hoped he would be able to go to school at the age of 6 years.

The visit to this hospital made the sixth visit to medical authorities in a two-year period. Two physicians had recommended institutionalization, yet had not taken time to discuss this with the mother. Two had recommended keeping the child at home, and yet did not offer the mother any insight into the nature of this disease or the prognosis for future development.

Mrs. H. stated that the pregnancy, labor and delivery of this child had been normal except for rather severe nausea and vomiting throughout the pregnancy. The boy was apparently normal at birth and no mention of Mongoloid features was made. He sat without support at 9-10 months and began to walk at 1½ years. About this time the child began crying at night and began getting out of bed to walk about the house or crawl in bed with his parents. He has done this until the present time, frequently getting up one to two times at night. He cries when put back to bed, thereby keeping both parents awake. There is no relationship between this and the amount of sleep the child has during the day.

The child was taken to a local physician at 2 years of age because the mother thought he was slightly retarded. The physician bluntly informed the mother that her child was a Mongolian idiot, that he would never be able to feed or dress himself, and that she should consider institutionalization for him. He suggested that a complete evaluation be made at a mental hygiene clinic. The information that the child was a Mongoloid came as a shock because of a previous experience the mother had in 1945 while serving as a WAC medical aide. She had cared for a badly retarded, seriously ill Mongoloid and had been rather appalled at this experience. Naturally, the news that her own child was similarly affected was difficult to accept.

Two months later a complete psychometric evaluation was done at the mental hygiene clinic. Again the mother was told that her son was a Mongolian idiot. It was suggested that the child be kept at home and be re-

evaluated at 6 years of age. No provision was made for the mother to return during the next four-year period.

One year ago, a year after the patient had been evaluated, the patient was taken to a pediatrician who very curtly told the mother that institutionalization was mandatory. He would not examine the child at that time so the mother made another appointment to see the same doctor for a complete examination of the patient. She states she hoped, after a complete examination, that he would suggest that she keep the child at home. The physician again refused to examine the patient or to discuss the problem with the mother. He stated, "I told you what to do and I don't want to see him again."

Six months ago, another doctor was consulted. He stated that the child was "not so bad," that he needed speech training and after this training would not need to be institutionalized. It was he who suggested bringing the patient to this hospital.

Mrs. H. was 30 years old when married and was 33 years of age when the patient was born. There are two siblings, ages 6 years and 17 months. Both of these children are apparently normal. Family history is completely negative, no other Mongoloid history being noted.

Past medical history was noncontributory.

In the psychiatric department a thorough work-up was done. The child's I. Q. was 40. He tested at 19 months of age. (His chronologic age was 48 months.) Since the parents lived in Maryland, no institutionalization was possible until the child was 6 years of age. Since the cost of private institutionalization was prohibitive in this case, they would have to keep the patient at home for another two years. Mongolism was fully discussed with regard to certainty of the diagnosis, prognosis for future development, life expectancy, effect of other normal children in the family and institutionalization in the future. Since it was felt this mother needed periodic reassurance, provision was made for the mother and child to be seen at six-month or yearly intervals at a mental hygiene clinic. This will also, we hope, prevent the mother from "shopping" for new physicians.

DISCUSSION

Reginald S. Lourie, M.D.

Dr. Wolf's description of what has gone on in this family in their struggles to deal with and understand the retardation in their child points up a not uncommon phenomenon. It would seem to indicate that an inquiry is in order into the impact on the family wherever there is a child with mental deficiency. The parents need help in thinking through what is involved in terms of their own way of living, how the other children in the family are involved, and what implications the defective child has in relation to the family's social standing, their position in their own families, and with their neighbors. It is important for them to know what their role has been in creating the deficiency so that misconceptions about what they may feel is their fault can be corrected. Considerable guilt often is present if these issues are not clear and it can push parents into what seem to be illogical degrees of defense of themselves or overprotection of the child—even to the extent of families isolating themselves from all contacts or hiding the child.

It is important for the parents to have some idea of what to expect from the child. Some of their chief concerns stem from problems such as how far will he be able to go in school and will he be able to ever live outside a protected environment. Will the child ever be able to read enough to know what is playing in the movies, or learn enough arithmetic so that he can make change and will not be taken advantage of in the community in money matters. Certainly, if we were discussing with the family the outlook and handling of any other kind of pediatric problem we would think with them in terms of what can be expected from and what limitations will be necessary for a child after any handicapping process. This problem is essentially no different.

Emphasis should be placed on the separation of intellectual from personality growth and development. It should be stressed with parents that mental deficiency does not mean that a child cannot grow to have normal social and personal development.

There seems to be a tendency to glibly pass off behavior distortions and distorted habit patterns on the basis of a child's defectiveness when, actually, these personality problems are as correctable in these children as they are in their brighter brothers and sisters. Certainly, with the vast majority of defective children, normal personality development can be achieved. Equipped with normal ability to establish relationships, to accept responsibility, and with a sound concept of right and wrong, morons have been demonstrated to make good community adjustments including good work adjustments and marital adjustments, and to make law-abiding citizens. Certainly, we as doctors, have a responsibility to foster the healthy development and adjustment of potentially useful citizens even if they are able to do only unskilled and menial work as adults. The tendency of too many people is to cross such children off the books early in life.

Institutionalization is sometimes too easily used as a solution as we can see from the above case, and parents are too infrequently prepared for it properly. There are very few institutions that will accept children under 5 or 6 years of age. If we realize at the same time that the maximum degree of personality development takes place in the first five or six years, we can see that the parents have something very important to accomplish in this time except in those defective children who are in the idiot and imbecile categories. Given the opportunity for normal personality development, the child can make a much better adjustment in the institution.

In every community there are agencies established that have trained personnel who are in a position to help the physician handle these aspects of the family's problem. There are also parent groups in many communities that can help provide facilities for training in the community. Part of the doctor's role is to know these agencies.

The physician dealing with the matter of prognosis with the parents of mentally defective children will want to call for specialized help such as the psychologist and social worker can provide. He would not be comfortable with establishing a program of long-term treatment for anemia because a child looks pale, without some laboratory confirmation and follow-up. The psychologist and social worker can provide considerable information for the doctor's use in understanding the degree of the problem, in dealing with family of the defective child, and in helping plan a program of future care in terms of resources available.